A COMPARATIVE STUDY OF LIPID LOWERING EFFECT OF AN ANTIOXIDANTS VITAMIN E AND COENZYME Q 10 WITH ATORVASTATIN IN DYSLIPIDAEMIC PATIENTS

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of

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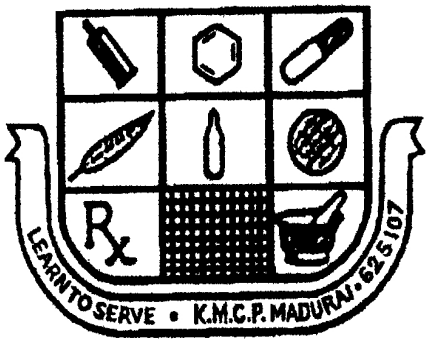

DEPARTMENT OF PHARMACY PRACTICE

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CERTIFICATE

This is a bonafide dissertation work entitled **"A COMPARATIVE STUDY OF LIPID LOWERING EFFECT OF AN ANTIOXIDANTS VITAMIN E AND COENZYME Q 10 WITH ATORVASTATIN IN DYSLIPIDAEMIC PATIENTS"** submitted by **Mr. LALITH KUMAR MOVVA** Reg. No. **261240055** to The Tamilnadu Dr. M. G. R. Medical University, Chennai, in partial fulfillment of the requirement for the award of Master of Pharmacy in Pharmacy Practice at K.M. College of Pharmacy, Madurai, is a work carried out by him during the year 2013-2014.

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CONTENTS

Introduction

Lipids, one of the most common factors, which determine the cardiac health, make a critical part in the research areas of cardiology. This does not mean that lipids are foes of human beings. Lipids, which include a wide variety of organic molecular chains, are inevitable for normal functioning of the body including the brain, joint mobilization and even energy production.[1] Different types of lipids do different things.

Lipids are very essential for absorption of fat-soluble vitamins. They coat cell membranes and allow normal cell development and functioning. Lipids are a form of stored energy, as the human body is more prone to fat storage, and supplies energy in emergencies. They act as inter-cellular messengers inducing enzyme and protein kinases production.[2] Hormone production in the body is normal until the lipids function normal.

If we have a look at the entire categorization of the lipids it will become clear that the fact, body requires lipids in enormous proportion when compared to other nutrients for healthy functioning of the body, is true.

Whenever there comes a swing of serum levels of lipids from the normal, then the body's normal functioning is disturbed and the health of the person get to be concerned. Persistent abnormal serum levels of lipids lead to coronary artery diseases, obesity and lot more. The serum lipid levels oscillate from the normal due to many factors including fatty diet and poor utilization of lipids by the body. This patho-physiological condition is said 'Dyslipidaemia'.

Dyslipidaemia

Dyslipidaemia is a broad term that refers to a number of lipid disorders that include increased as well as decreased levels of serum lipid. It is widespread and imposes substantial costs on the healthcare system. Research over the past 4 decades has consistently shown the burden of dyslipidaemia to be very high in terms of morbidity, mortality and medical costs.[3]

Dyslipidaemia is an important major risk factor for coronary heart disease(CHD).The world health organization estimates that dyslipidaemia is associated with more than half of global cases of ischaemic heart disease and more than 4 million deaths per year. Over 7.2 million people die from coronary heart diseases worldwide, more than from cancer or infectious causes.[4]

Epidemiological evidences state that every 1 % increase in LDL leads to 1% increase in risk for CHD, also, every 1 % increase in HDL leads to 2-3 % reduction of risk for CHD.[5] 80 % lipid disorders are related to diet and lifestyle, although familial disorders are important as well.

The basic categories of dyslipidaemias include elevated low-density lipoprotein (LDL), low high-density lipoprotein (HDL), excess lipoprotein (a), hypertriglyceridaemia, atherogenic dyslipidaemia and mixed lipid disorders. Most patients with CHD have mixed dyslipidaemia (e.g., elevated LDL and low HDL), which is also commonly seen in patients with diabetes mellitus (DM). A complete overview of the classification of dyslipidaemias gives a clear cut image of the different types of lipid disorders.

Classification of Dyslipidaemia

Dyslipidaemia is usually classified on the basis of Phenotype or Etiology Phenotype implies the presentation of dyslipidaemia in the body including the specific type of lipid whose level has increased or decreased. Etiology implies the reason for dyslipidaemia, whether, it is genetic or secondary to other pathophysiological conditions. Basically, dyslipidaemia includes abnormal levels of both lipids and, of course, lipoproteins.

The Fredrickson classification[6] is a perfect example of the phenotypic classification, although it is not used now. Fredrickson gives five phenotypes of dyslipidaemia. Table 1 represents that.

Table 1. Fredrickson Phenotypes

Phenotype	**Elevated Lipoproteins**	**Elevated Lipids**
I	Chylomicrons	TG
II a	LDL	Cholesterol
II b	LDL and VLDL	TG and Cholesterol
III	VLDL, IDL and Chylomicron Remnants	TG and Cholesterol
IV	VLDL	TG
V	VLDL and Chylomicrons	TG and Cholesterol

LDL: Low Density Lipoproteins; VLDL: Very Low Density Lipoproteins; TG: Triglycerides; IDL: Intermediate Density Lipoproteins

Even though, the phenotypic classification is simple and clear, a much more informative classification which involves the primary and the secondary reasons of dyslipidaemia becomes necessary. Table 2 gives a clear picture of the Etiologic classification[7] of dyslipidaemia.

Table 2.Classification of Dyslipidaemia

Name	**Lipid(s) & Lipoprotein(s) In Excess**	**Possible Cause(s) For Elevated Levels**
Polygenic Hypercholesterolaemia	LDL,Cholesterol	Nutritional, Genetic(less active LDL receptors)
Familial Hypercholesterolaemia	LDL,Cholesterol	Genetic(defective gene for the LDL receptors)
Diet-induced Hypertriglyceridaemia	VLDL & TG	Excess intake of calories, alcohol
Primary Hpertriglyceridaemia	VLDL, TG & LDL	Diet(often associated with other medical problems like obesity, diabetes)
Secondary Hypertriglyceridaemia	VLDL & TG	Secondary to other medical problems like obesity,diabetes,nephritic syndrome
Familial Combined Hyperlipidaemia	VLDL, TG & LDL	Genetic(overproduction of apolipoprotein B-100)
Lipoprotein Lipase Deficiency	Chylomicrons, TG & VLDL	Genetic(Lipoprotein Lipase enzyme deficiency)

LDL: Low Density Lipoproteins; VLDL: Very Low Density Lipoproteins; TG: Triglycerides; HDL: High Density Lipoproteins

In short, the etiology of dyslipidaemia can be explained such that primary dyslipidaemia are due to genetic make-up and secondary dyslipidaemia are due to sedentary life-style and other underlying pathophysiological conditions.

Primary dyslipidaemia are most seen in children than in adults. They are the consequences of gene mutations.[8]

Secondary causes contribute to dyslipidaemia in most of the adults. It's just primarily because of sedentary life-style. Consumption of diet containing saturated fats, cholesterol and trans fats results in increased levels of lipids in the blood. Apart from diet, medical problems like diabetes, chronic kidney disease, hypothyroidism, primary biliary cirrhosis, other cholestatic liver diseases and alcohol overuse also contribute to dyslipidaemia. Usage of drugs such as thiazides, β-blockers, retinoids, highly active anti-retroviral agents, oestrogen and progestins, and glucocorticoids infact cause dyslipidaemia.[9]

The classifications alone don't give a perfect idea about the lipids and the lipoproteins involved in the human physiology, for clinically managing dyslipidaemia. A closer view in to the Cholesterol Homeostasis gives a better picture of the lipid transportation and utilization systems.

Cholesterol Homeostasis[10]

Cholesterol is the lipid that primarily serves as the precursor to steroid hormones and bile acids, and as the main component of cell membranes. Cholesterol required for normal functioning of the body is manufactured in the body and also ingested from exogenous dietary sources. Cholesterol levels in the blood reflect approximately 40% to 60% endogenous cholesterol, with the balance coming from dietary

sources. Triglycerides, which are composed of fatty acids esterified to glycerol and used as energy substrates, are supplied by fats in the diet and through the conversion of carbohydrates by the liver.

Cholesterol, triglycerides, and other lipids in the body are transported as spherical particles, through the bloodstream, called lipoproteins.

Lipoproteins can be divided in to five major categories depending on their composition. Table 3 depicts that.

Table 3.Characteristics of the Major Classes of Lipoproteins

Lipoproteins	Composition	Origin
Chylomicrons	Exogenous/Dietary triglycerides	Gut
Very-low-density-lipoproteins(VLDL)	Triglycerides	Liver
Intermediate-density lipoproteins(IDL)	Cholesterol esters & Triglycerides	VLDL/HDL Catabolism
Low-density lipoproteins(LDL)	Cholesterol	VLDL Catabolism
High-density lipoproteins(HDL)	Cholesterol	Liver & Gut

The classes from largest and least dense to smallest and most dense are chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). The larger, more floating particles primarily have a triglyceride-rich core, while the smaller, and denser particles have a cholesterol ester core.LDL accounts for approximately

60% to 70% of total serum cholesterol and is the primary atherogenic class of lipoproteins.HDL constitutes approximately 20% to 30% of total serum cholesterol with VLDL comprising about 10% to 15%.

Two main sources supply cholesterol to the body. It is obtained exogenously from the systemic circulation and endogenously via intracellular synthesis. The systemic circulatory system is responsible for the synthesis, transportation, and catabolism of chylomicron particles and remnants.

The lipids which are digested and absorbed in the proximal small bowel are then converted to chylomicrons by the cells in the intestinal endothelium. Thus, chylomicrons basically contain lipids, fatty acids, cholesterol, and apolipoproteins, obtained from diet. These chylomicrons then enter the lymphatic system and get converted to chylomicron remnants, which are smaller,and contain less fatty acids, and apolipoproteins B-48 and E. These remnants are then cleared from the circulation by the LDL-related receptor protein found in the liver.

In addition to utilizing circulating lipoproteins from exogenous sources, cells can also synthesize their own cholesterol through the endogenous pathway. The intracellular cholesterol synthesis involves a series of biochemical reactions starting with acetyl-CoA. The enzyme HMG-CoA synthetase, catalyzes the conversion of acetyl-CoA to HMG-CoA. The other one, HMG-CoA reductase, catalyzes the conversion of hepatic HMG-CoA to mevalonic acid, which is used in a later step in the biosynthesis of cholesterol.

Fatty acids and cholesterol produced by the body are then transported through the endogenous pathway with the help of three major lipoproteins,VLDL, LDL, and HDL. Triglycerides are synthesized in liver, especially in the presence of excess carbohydrates, and later

drained into the bloodstream as VLDL. VLDLs contain approximately five times more triglycerides than cholesterol.

Once released into the bloodstream, triglyceride molecules in the VLDL particles are hydrolysed and used for energy production, primarily by heart and skeletal muscle, or stored in fat cells. The VLDL particles, are then cleared via
the hepatic remnant receptor, or by further release of triglycerides resulting in the formation of IDL particles.

The triglceride content of IDL is nearly the same as VLDL. Lipolysis continues leading to much smaller, cholesterol-rich LDL particles. IDL particles have a short life span. Their cholesterol and triglyceride contents do not significantly influence cholesterol measurements. Less than 5% of cholesterol circulates in IDL particles, but in certain cases it is not. 50% of IDL particles are cleared from the circulation by the LDL receptor while the remaining is converted to LDL particles.

LDL is the primary atherogenic lipoprotein, and the smaller the size of the LDL particle, the more it is able to penetrate into sub-endothelial tissue, where it contributes to the development of atherosclerosis. Excessive circulating LDL cholesterol will lead to atherogenic plaque formation in the vascular endothelium, potentially leading to coronary artery disease (CAD).

Two types of physiologically important LDL particles have been recently identified to be highly associated with CHD risk. The first, lipoprotein (a) [Lp (a)] particle, and the other one is atherogenic lipoprotein phenotype B. This subclass is found in approximately 30% of the population and is associated with a high risk of CHD.

Another physiologically important lipoprotein involved in the endogenous pathway is HDL. HDL particles are rich in cholesterol like

LDL,but very small. HDL is involved in reverse cholesterol transport, causing an antiatherogenic effect. Efficiently, HDL may prevent or remove cholesterol deposits within the arterial wall.

Other beneficial roles of HDL cholesterol are

1. Preventing LDL oxidation by acting as an antioxidant
2. Reducing platelet aggregability by increasing prostacyclin production
3. Stabilizing serum prostacyclin and promotes fibrinolysis
4. Competitively inhibiting the uptake of LDL by endothelial cells
5. Preventing LDL aggregation and uptake by macrophages
6. Decreasing cholesterol and foam cell formation
7. Inhibiting platelet activation by LDL through the phosphatidylinositol cycle

An important marker for abnormal metabolism of chylomicrons and VLDL particles is, as triglycerides increase, HDL decreases. Cholesterol found in VLDL and IDL particles are transported to the liver for elimination.

HDL, LDL, and VLDL are involved in the transport of triglycerides and cholesterol from the liver to the body where they may be used by cells and from the body to the liver where they may be eliminated. The cell will up-regulate its synthesis of the LDL receptor, when the amount of cholesterol is insufficient to meet the requirements of any cell. This LDL receptor will migrate to an area on the surface of the cell called the 'coated pits'.

Once in the coated pits, the cell recognizes circulating lipoproteins VLDL, IDL, and LDL particles. Since, both the VLDL and IDL particles contain both B and E proteins they may have a higher binding affinity for the LDL receptor than the LDL particles.

Immediately after getting bound the lipoproteins are internalized by the cell, and taken up by the liposomes, and then broken down to get used by the cell. The same process continues to maintain homeostasis.

Link between Lipids and CHD

Atherosclerosis is the inflammatory process which is responsible for the risk of CHD. Lipids are known to have an important role in developing an atherosclerotic plaque.

With advancing age, as changes occur within the blood vessel wall, other "intruders" enter into the battle.[11] These "intruders" are constituents of the atherosclerotic process, which has some aspects in common with the aging process. However, unlike the aging process within blood vessels, atherosclerosis includes cholesterol accumulation and recruitment of other blood cells to join the battle. These cells are called 'the inflammatory cells'.

Atherosclerosis is so common in older persons such that at least one out of two persons over sixty five years of age has atherosclerosis. It was previously thought that it was part of the "normal aging process". An alternate view is that atherosclerosis is a disease process that takes advantage of the changes that occur within the artery with aging.

The vascular aging process and the atherosclerotic process go hand-in-hand, and they influence each other. The more severe the vascular aging process, the easier it is for atherosclerosis to take power; the more severe your atherosclerosis, the bigger its impact on the vascular aging.

Thus, it appears that the atherosclerosis process and the aging process make situations together to enable the disease called atherosclerosis to be more visible and more severe in older persons.

The risk factors of atherosclerosis seem to be, [12]

1. Diabetes
2. Alcohol over-use
3. Raised blood pressure readings
4. Increased blood cholesterol levels
5. High-fat diet
6. Increasing age
7. Obesity
8. Personal or family history of heart disease
9. Smoking

In recent years, it has become apparent that atherosclerosis is a chronic inflammatory process affecting large- and medium-sized arteries throughout the cardiovascular system. The rate of progression is variable with the lesions occurring primarily at sites of low shear stress or increased turbulence, i.e., at sites of bifurcation or curvature of the vessels.

The early stages of atherosclerosis are also similar to the reactions noted in asthma and consist of infiltration of the affected site by T lymphocytes and monocytes, which then transform into macrophages (foam cells), followed by proliferation of fibrous tissue. Eventually in its natural progression, calcification of the atheromatous plaque occurs. Minimal calcification is present even in the "soft plaque."

Pathogenesis of Plaque Formation[13]

The herald lesion in the arteries is endothelial dysfunction triggered by exposure of the endothelium to one or more of the following agents.

1. Oxidized LDL particles
2. Free radicals
3. Elevated plasma homocysteine - an inborn error of metabolism
4. Local genetic alteration
5. Chronic systemic infection - Herpes viruses, Chlamydia Pneumonia, Helicobacter pylori

Initially the endothelium attempts to repair itself by attracting T-lymphocytes, monocytes and platelets to the injured site. When the reparative process fails, the endothelium becomes permeable and the lymphocytes and monocytes migrate into the deep layer of the intima where a series of reactions occur attracting LDL particles to the site. These particles are engulfed by monocytes, which are then transformed into macrophages (foam cells). Smooth muscle cells begin migrating from the media, and the fatty streak is formed. This stage is a reversible one.

As the attempt at endothelial repair progresses, a fibrous cap consisting of smooth muscle and collagen is formed. At the same time, the macrophages and monocytes involved in the original reaction begin to die resulting in the formation of a necrotic core covered by the fibrous cap.

The lesions, atheromatous plaques, continue to enlarge as leucocytes and lipid fragments enter the lesions at the shoulders, which are the most vulnerable sites on the plaque.

While the atheroma is increasing in size, the wall of the artery expands due to the presence of the elastic tissue in the media in an ongoing remodelling process. At the same time, small blood vessels (vasa vasorum) develop to maintain the viability of the plaque. Eventually the arterial wall can no longer expand, and the plaque begins to bulge into the vessel lumen. As a result of the remodelling process, the presence of the atheromatous plaque is not recognized by angiography until the plaque occupies up to 45% of the vessel wall and luminal blood flow is compromised.

When the process continues, there is thinning of the fibrous cap accompanied by fissuring of the endothelial surface. The occurrence of several fissures can contribute to overt plaque rupture although the attempt at maintaining a balance between rupture and repair continues. When the rate of fissuring surpasses the rate of repair, overt plaque rupture occurs usually at the shoulder of the plaque.

With the rupture of the plaque, its contents consisting of lipid fragments and cellular debris are released into the vessel lumen. The shearing force may also result in rupture of the small vessels in the plaque. These are exposed to thrombogenic agents on the endothelial surface resulting in thrombus formation. If the thrombus formed is large enough, luminal occlusion occurs resulting in a "hard event" (myocardial infarction or stroke).

The process described outlines the genesis of soft plaque rupture, which accounts for more than 50% of sudden cardiac or cerebrovascular events. Among individuals experiencing these events, warning signs are rare, and outcomes are frequently catastrophic.

Effects of Atherosclerosis

Effects develop very gradually.[14]Many times, people with atherosclerosis have no symptoms until an artery is 40% clogged with plaque. Symptoms differ widely depending upon which arteries are affected.

Coronary Artery Disease[15]

The heart has its own arteries, the coronary arteries, so that it can pump oxygenated blood to itself. If an artery is so narrow, part of the heart may not get enough blood during increased physical activity. The consequence is chest pain that goes away with rest. This chest pain is technically called 'stable angina'.

It becomes unstable, when there is more frequent chest pain with less physical activity than before or chest pain even at rest.

In the worst scenario, the plaque ruptures and platelets aggregate at the site, large enough to obstruct blood flow significantly. Cardiac muscle downstream would be deprived of blood and soon it dies. This is what we say Myocardial Infarction. Otherwise, 'heart attack'. Scar tissue eventually develops at the site of infarction and takes the place of muscle.

The heart becomes weaker overall, paving way to congestive heart failure down the line. Scarring can also affect the heart's electrical system, producing one of many possible abnormal heart rhythms.

Disease Cerebrovascular

Cerebrovascular diseases, where the arteries that supply the brain with blood are narrowed, can cause transient ischemic attack (a sudden loss of brain function with complete recovery within 24 hours) and stroke. Symptoms may include weakness or paralysis on one side of the body, trouble speaking or understanding speech, loss of vision in one eye, muscle weakness, sudden trouble walking, dizziness, loss of balance or coordination, and sudden severe headache.

Abdominal Aortic Aneurysm[16]

Plaques can form in the aorta, the large artery coming up the heart and down through the chest and abdomen. Atherosclerosis in the abdominal aorta weaken the artery wall so that pressure from the blood can stretch a wall segment like a balloon. This is called an aneurysm. If it widens enough, there is a risk of rupture and bleeding requiring surgical intervention.

Mesenteric Ischemia

The mesenteric arteries supply the intestines and they, too, can be prone to decreased blood flow from atherosclerosis. The result is either temporary abdominal pain with eating or longer lasting pain when an artery is completely occluded and a segment of intestine dies. While this is rare, the consequences can be serious and life-threatening. With intestinal tissue death, bacteria that normally live in the intestines can make its way into the bloodstream or into the abdominal cavity if the intestine perforates. Intestinal bleeding is another complication.

Peripheral Artery Disease[17]

Peripheral artery disease affects the arteries that supply the arms and legs with oxygen-rich blood. Symptoms may include pain, aching, cramps, numbness or sense of fatigue in the leg muscles (intermittent claudication),"Bruits" (blowing sounds your doctor can hear with a stethoscope that indicate turbulence in blood flow),hair loss, thickened nails, smooth and shiny skin surface, skin that is cold to the touch, and gangrene.

Clinical Aspects of Dyslipidaemia[18]

Symptoms & Signs of Dyslipidaemia

Dyslipidaemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (CAD) and peripheral arterial disease. High levels of TGs (> 1000 mg/dL [> 11.3 mmol/L]) can cause acute pancreatitis. High levels of LDL can cause eyelid xanthelasmas; arcus corneae; and tendinous xanthomas at the achilles, elbow, and knee tendons and over metacarpophalangeal joints.

Patients with the homozygous form of familial hypercholesterolaemia may have the above findings plus planar or cutaneous xanthomas. Patients with severe elevations of TGs can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet. Patients with the rare dysbetalipoproteinaemia can have palmar and tuberous xanthomas.

Severe hypertriglyceridaemia (> 2000 mg/dL [> 22.6 mmol/L]) can give retinal arteries and veins a creamy white appearance (lipaemia retinalis). Extremely high lipid levels also give a lactescent (milky) appearance to blood plasma. Symptoms can include paraesthesias, dypsnoea, and confusion.

Dyslipidaemia is linked to many diseases like heart disorders, high blood pressure, and diabetes. The latest research shows that dyslipidaemia is also linked to erectile dysfunction. According to research, 20% of men who suffer from erectile dysfunction have dyslipidaemia.

Diagnosis of Dyslipidaemia

Serum Lipid Profile (measured total cholesterol, TG, and HDL-cholesterol and calculated LDL-cholesterol and VLDL)

Dyslipidaemia is suspected in patients with characteristic physical findings or complications of dyslipidaemia (e.g., atherosclerotic disease). Primary lipid disorders are suspected when patients have physical signs of dyslipidaemia, onset of premature atherosclerotic disease (at < 60 yr), a family history of atherosclerotic disease, or serum cholesterol > 240 mg/dL (> 6.2 mmol/L). Dyslipidaemia is diagnosed by measuring serum lipids. Routine measurements (lipid profile) include total cholesterol (TC), TGs, HDL-cholesterol, and LDL-cholesterol.

Lipid profile measurement

TC, TGs, and HDL-cholesterol are measured directly. TC and TG values reflect cholesterol and TGs in all circulating lipoproteins, including chylomicrons, VLDL, IDL, LDL, and HDL. TC values vary by 10% and TGs by up to 25% day-to-day even in the absence of a disorder. TC and HDL-cholesterol can be measured in the nonfasting state, but most patients should have all lipids measured while fasting for maximum accuracy and consistency.

Testing should be postponed until after resolution of acute illness, because TGs increase and cholesterol levels decrease in inflammatory states. Lipid profiles can vary for about 30 days after an

acute MI. However, results obtained within 24 h after MI are usually reliable enough to guide initial lipid-lowering therapy.

LDL-cholesterol values are most often calculated as the amount of cholesterol not contained in HDL and VLDL. VLDL is estimated by TG ÷ 5, because the cholesterol concentration in VLDL particles is usually $^{1}/_{5}$ of the total lipid in the particle. Thus, LDL-cholesterol = TC − [HDL-cholesterol + (TGs ÷ 5)] (Friedewald formula). This calculation is valid only when TGs are < 400 mg/dL and patients are fasting, because eating increases TGs. The calculated LDL-cholesterol value incorporates measures of all non-HDL, nonchylomicron cholesterol, including that in IDL and Lp (a).

LDL can also be measured directly using plasma ultracentrifugation, which separates chylomicrons and VLDL fractions from HDL and LDL, and by an immunoassay method. Direct measurement may be useful in some patients with elevated TGs, but these direct measurements are not routinely necessary.

The role of apo B testing is under study because values reflect all non-HDL cholesterol (in VLDL, VLDL remnants, IDL, and LDL) and may be more predictive of CAD risk than LDL alone.

Other tests

Patients with premature atherosclerotic cardiovascular disease, cardiovascular disease with normal or near-normal lipid levels, or high LDL levels refractory to drug therapy should probably have Lp (a) levels measured. Lp (a) levels may also be directly measured in patients with borderline high LDL-cholesterol levels to determine whether drug therapy is warranted. C-reactive protein and homocysteine measurement may be considered in the same populations.

Secondary causes

Tests for secondary causes of dyslipidaemia including measurements of fasting glucose, liver enzymes, creatinine, thyroid stimulating hormone (TSH), and urinary protein should be done in most patients with newly diagnosed dyslipidaemia and when a component of the lipid profile has inexplicably changed for the worse.

Screening

A fasting lipid profile (TC, TGs, HDL-cholesterol, and calculated LDL-cholesterol) should be obtained in all adults ≥ 20 yr and should be repeated every 5 yr. Lipid measurement should be accompanied by assessment of other cardiovascular risk factors, defined as diabetes mellitus, cigarette use, hypertension, family history of CAD in a male 1st-degree relative before age 55 or a female 1st-degree relative before age 65.

A definite age after which patients no longer require screening has not been established, but evidence supports screening of patients into their 80s, especially in the presence of atherosclerotic cardiovascular disease.

Indications for screening patients < 20 yr are atherosclerotic risk factors, such as diabetes, hypertension, cigarette smoking, and obesity; premature CAD in a parent, grandparent, or sibling; or a cholesterol level > 240 mg/dL (> 6.2 mmol/L) or known dyslipidaemia in a parent. If information on relatives is unavailable, as in the case of adopted children, screening is at the discretion of the health care practitioner.

Patients with an extensive family history of heart disease should also be screened by measuring Lp (a) levels.

Treatment

Treatment is indicated for all patients with cardiovascular disease (secondary prevention) and for some without (primary prevention). The goal of treating hyperlipidaemia is to prevent or reduce the risk and complications of cardiovascular disease. Lipid-lowering therapy reduces the risk of CHD in high-risk individuals. Clinical trials have shown reductions of about 30% in relative risk of CHD events and 20% for relative risk of death.

The National Institutes of Health's National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines (Table 4 and Table 5) are the most common reference for deciding which adults should be treated. The guidelines focus primarily on reducing elevated LDL-cholesterol levels and secondarily on treating high TGs, low HDL, and metabolic syndrome.

An alternate treatment guide (the Sheffield table) uses TC: HDL ratios combined with presence of CAD risk factors to predict cardiovascular risk, but this approach probably leads to undertreatment.

Treatment of children is controversial; dietary changes may be difficult to implement, and no data suggest that lowering lipid levels in childhood effectively prevents heart disease in adulthood. Moreover, the safety and effectiveness of long-term lipid-lowering treatment are questionable. Nevertheless, the American Academy of Pediatrics (AAP) recommends treatment for some children who have elevated LDL-cholesterol levels.

Treatment options depend on the specific lipid abnormality, although different lipid abnormalities often coexist. In some patients, a single abnormality may require several therapies; in others, a single

treatment may be adequate for several abnormalities. Treatment should always include treatment of hypertension and diabetes, smoking cessation, and in patients with a 10-yr risk of MI or death from CAD of ≥ 10% with low-dose daily aspirin. In general, treatment options for men and women are the same.

Table 4.National Cholesterol Education Program Adult Treatment Panel III Approach to Dyslipidemias

1. Measure fasting lipoproteins (in mg/dL):

TC (mmol/L)

< 200 (<5.17)	-	Desirable
200–239 (5.17–6.18)	-	Borderline high
≥ 240 (≥ 6.20)	-	High

LDL-cholesterol

< 100 (<2.58)	-	Optimal
100–129 (2.58–3.33)	-	Near optimal/above optimal
130–159 (3.36–4.11)	-	Borderline high
160–189 (4.13–4.88)	-	High
≥ 190 (≥ 4.91)	-	Very high

HDL- Cholesterol

< 40 (< 1.03)	-	Low
≥ 60 (≥ 1.55)	-	High

TG

< 150 (< 1.695)	-	Desirable
150–199 (1.695–2.249)	-	Borderline high
200–499 (2.26–5.639)	-	High
≥ 500 (≥ 5.65)	-	Very high

2. Identify CAD or CAD equivalents.

1. Peripheral arterial disease
2. Abdominal aortic aneurysm
3. Symptomatic carotid artery disease
4. Diabetes mellitus
5. Additional risk factors that confer 10-yr risk of MI or CAD death >20%

3. Identify major CAD risk factors.

1. Cigarette smoking
2. Hypertension (BP ≥ 140/90 *or* on antihypertensive drug)
3. Low HDL (≤ 40 mg/dL [1.03 mmol/L])
4. 4.Family history of premature CAD (CAD in male 1st-degree relative < 55 or in female 1st-degree relative < 65)
5. Age (men ≥ 45, women ≥ 55)

CAD: Coronary Artery Disease; LDL: Low Density Lipoproteins; TG: Triglycerides; HDL: High Density Lipoproteins; TC: Total Cholesterol

Table 5. NCEP Adult Treatment Panel III Guidelines for Treatment of Hyperlipidemia

Risk Category	Begin Lifestyle Changes If	Consider Drug Therapy If	LDL Goal
High: CAD or CAD equivalents (10-yr risk > 20%)	LDL ≥ 100 mg/dL (≥ 2.58 mmol/L)	LDL ≥ 100 mg/dL (≥ 2.58 mmol/L) Drugs optional if LDL < 100 mg/dL [< 2.58 mmol/L]) < 100 mg/dL < 70 mg/dL optional	
Moderate high : ≥ 2 risk factors with 10-yr risk 10 to 20%	LDL ≥ 130 mg/dL (≥ 3.36 mmol/L)	LDL ≥ 130 mg/dL (≥ 3.36 mmol/L)	< 130 mg/dL < 100 mg/dL optional
Moderate : ≥ 2 risk factors with 10-yr risk < 10% LDL ≥ 130 mg/dL (≥ 3.36 mmol/L)	LDL ≥ 160 mg/dL (≥ 4.13 mmol/L)	< 130 mg/dL < 100 mg/dL optional Lower	
Lower : 0–1 risk factor	LDL ≥ 160 mg/dL (≥ 4.13 mmol/L)	LDL ≥ 190 mg/dL (≥ 4.91 mmol/L) Drug optional if LDL 160–189 mg/dL [4.13–4.88 mmol/L])	< 160 mg/dL

CAD: Coronary Artery Disease; LDL: Low Density Lipoproteins;

Treatment for Elevated LDL-Cholesterol

In adults, ATPIII guidelines recommend treatment for those with any of the following:

1. Elevated LDL-cholesterol levels and a history of CAD
2. Conditions which confer a risk for future cardiac events similar to that of CAD itself (CAD equivalents, defined as diabetes mellitus, abdominal aortic aneurysm, peripheral arterial disease, and symptomatic carotid artery disease)
3. ≥ 2 CAD risk factors

ATPIII guidelines recommend that these patients have LDL-cholesterol levels lowered to < 100 mg/dL, but accumulating evidence suggests that this target may be too high and a target LDL-cholesterol < 70 mg/dL is an option for patients at very high risk (e.g., patients with known CAD and diabetes, other poorly controlled risk factors, metabolic syndrome, or acute coronary syndrome). When drugs are used, a dose providing at least a 30 to 40% decrease in LDL-cholesterol is desirable.

For children, the AAP recommends dietary treatment for children with LDL-cholesterol > 110 mg/dL. Drug therapy is recommended for children > 8 yr and with either of the following:

1. Poor response to dietary therapy, LDL-cholesterol ≥ 190 mg/dL, and no family history of premature cardiovascular disease
2. LDL-cholesterol ≥ 160 mg/dL and a family history of premature cardiovascular disease or ≥ 2 risk factors for premature cardiovascular disease

Childhood risk factors besides family history and diabetes include cigarette smoking, hypertension, low HDL-cholesterol (< 35 mg/dL), obesity, and physical inactivity.

Treatment options to lower LDL-cholesterol in all age groups include lifestyle changes (diet and exercise), drugs, dietary supplements, procedural interventions, and experimental therapies. Many of these options are also effective for treating other lipid abnormalities. Exercise lowers LDL-cholesterol in some people; it is also essential to maintain ideal body weight. Dietary changes and exercise should be the initial approach whenever feasible.

Non-drug Therapy[19]

Diet can decrease both cholesterol and triglyceride levels.

1. Total fat intake should be 30% or less of total energy intake.
2. Saturated fats should be 10% or less of total energy intake.
3. Dietary cholesterol should be less than 300 mg/day.
4. Saturated fats should be replaced by monounsaturated or polyunsaturated fats.
5. Five portions of fruit and vegetables should be eaten per day.
6. Two portions of fish should be eaten per week, including a portion of oily fish.
7. Advice pregnant women to limit their intake of oily fish to two portions a week.
8. Do not routinely recommend omega-3 fatty acid supplements or plant sterols and stanols for primary prevention.

Other appropriate measures include weight reduction, regular physical exercise, and, when appropriate, additional measures to reduce cardiovascular risk such as smoking cessation, alcohol reduction and blood pressure and blood glucose control.

Lifestyle changes can involve diet and exercise. Dietary changes include decreasing intake of saturated fats and cholesterol; increasing the proportion of dietary fibre, and complex carbohydrates; and maintaining ideal body weight. Referral to a dietitian is often useful, especially for older people. The length of time for which lifestyle changes should be attempted before beginning lipid-lowering drugs is controversial. In patients at average or low cardiovascular risk, 3 to 6 months is reasonable. Generally, 2 to 3 visits with a patient over 2 to 3 months are sufficient to assess motivation and adherence.

Drug Therapy

Drugs are the next step when lifestyle changes are not effective. However, for patients with extremely elevated LDL-cholesterol (> 200 mg/dL [> 5.2
mmol/L]) and those at high cardiovascular risk, drug therapy should accompany diet and exercise from the start.

Table 6. Lipid Lowering Drugs

Drug	Primary Mechanism Of Action	Usual Daily Dose	Side Effects
Statins(Atorvastatin,Simvastatin Lovastatin, Rosuvastatin…)	↑LDL receptors, ↑LDL and VLDL catabolism	Variable	GI,constipation, flatulence,dyspeps-ia,headache
Fibrates(Fenofibrate,Gemfibrozil , Bezafibrate…)	↑VLDL catabolism	600 mg twice a day	GI,myalgias,incre-ased liver function tests
Nicotinic acid (niacin) ↑LDL catabolism	2-3 grams three times a day	GI,flushing, hepato-toxicity,prur itus	
10 mg once a dayMyalgia,abdominal discomfortBile acid sequestrants (Colestipol, Choles-tyramine…)	↑LDL metabolism	12-30 grams in 2-4 divided doses	Constipation, bloat-ing,abdominal pain, gas
Dietary supplements (Vitamin E, omega-3 fatty acids…)↓Cholesterol absorption Cholesterol absorption inhibitor(Ezetimibe)	↓Lipid peroxidation	3-4 gram daily	No serious side effects

↑: Increases; ↓: Decreases; GI: Gastro-Intestinal; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein;

Statins are the drugs and possibly treatment of choice for LDL-cholesterol reduction; they demonstrably reduce cardiovascular mortality. Statins inhibit hydroxymethylglutaryl CoA reductase (HMG CoA reductase inhibitor), a key enzyme in cholesterol synthesis, leading to up-regulation of LDL receptors and increased LDL clearance. They reduce LDL-cholesterol by up to 60% and produce small increases in HDL and modest decreases in TGs. Statins also appear to decrease intra-arterial inflammation, systemic inflammation, or both by stimulating endothelial nitric oxide production and may have other beneficial effects.

Adverse effects are rare but include liver enzyme elevations and myositis or rhabdomyolysis. Muscle toxicity without elevation in enzyme levels has also been reported. Older patients, patients with several disorders, and patients taking several drugs are susceptible to ADRs.

In some patients, changing from one statin to another or lowering the dose relieves the problem. Muscle toxicity seems to be most common when some of the statins are used with drugs that inhibit cytochrome P3A4 (e.g., macrolide antibiotics, azole antifungals, cyclosporine) and with fibrates, especially gemfibrozil. The preference of drug should be based on patient characteristics, LDL-cholesterol level, and provider discretion.

Bile acid sequestrants act by blocking intestinal bile acid reabsorption, forcing up-regulation of hepatic LDL receptors to recruit circulating cholesterol for bile synthesis. Cardiovascular mortality goes down when they are taken. Bile acid sequestrants are usually used with statins or with nicotinic acid to augment LDL-cholesterol reduction and are the drugs of choice for children and women who are or are planning to become pregnant.

Bile acid sequestrants are safe, but may cause adverse effects like bloating, nausea, cramping, and constipation. They may also increase TGs, so they are contraindicated in patients with hypertriglyceridaemia. Cholestyramine and colestipol, but not colesevelam, interfere with absorption of other drugs, notably thiazides, β-blockers, warfarin, digoxin, and thyroxine,an effect that can be decreased by administration 4 h before or 1 h after other drugs.

Cholesterol absorption inhibitors, such as ezetimibe, inhibit intestinal absorption of cholesterol and phytosterol. Ezetimibe usually lowers LDL-cholesterol by 15 to 20% and causes small increases in HDL and a mild decrease in TGs. Ezetimibe can be used as monotherapy in patients intolerant to statins or added to statins for patients on maximum doses with persistent LDL-cholesterol elevation. ADRs are very uncommon.

Dietary supplements like fibre supplements and commercially available margarines and other products containing plant sterols (sitosterol and campesterol) or stanols lower LDL-cholesterol levels. The latter reduce LDL-cholesterol by up to 10% without affecting HDL or TGs by competitively displacing cholesterol from intestinal micelles.

Procedural approaches are used in patients with severe hyperlipidaemia (LDL-cholesterol > 300 mg/dL) that is refractory to conventional therapy, such as occurs with familial hypercholesterolaemia. Options include LDL aphaeresis (in which LDL is removed by extracorporeal plasma exchange), ileal bypass (to block reabsorption of bile acids), liver transplantation (which transplants LDL receptors), and portocaval shunting (which decreases LDL production by unknown mechanisms). LDL aphaeresis is the procedure of choice in most instances when maximally tolerated therapy fails to lower LDL adequately. Aphaeresis is also the usual

therapy in patients with the homozygous form of familial hypercholesterolaemia who have limited or no response to drug therapy.

Future therapies to reduce LDL include peroxisome proliferator–activated receptor agonists that have thiazolidinedione-like and fibrate-like properties, LDL-receptor activators, LPL activators, and recombinant apo E. Cholesterol vaccination (to induce anti-LDL antibodies and hasten LDL clearance from serum) and gene transfer are theoretically interesting therapies that are under study but currently unavailable.

Treatment for Elevated Triglycerides (TG)

Though it is unclear if elevated TG independently contribute to cardiovascular disease, they are associated with multiple metabolic abnormalities that contribute to CAD (e.g. metabolic syndrome, DM). It can be said that lowering elevated TGs is beneficial. No target goals exist, but levels < 150 mg/dL (< 1.7 mmol/L) are generally considered desirable. Treatment of elevated TGs in children does not include any special precaution.

The overall treatment strategy is to first execute lifestyle changes, including exercise, weight loss, and avoidance of concentrated dietary sugar and alcohol. Intake of 2 to 4 servings/week of marine fish high in ω-3 fatty acids may be effective, but the amount of ω-3 fatty acids is often lower than needed; supplements may be helpful. In diabetic patients, glucose levels should be strictly controlled. If these measures are unsuccessful, lipid-lowering drugs should be considered. Patients with very high TGs should be given drug therapy immediately at diagnosis to more quickly reduce the risk of acute pancreatitis.

Fibrates reduce TGs by around 50%. They appear to decrease hepatic VLDL synthesis. Also hike up HDL by up to 20%. Fibrates may cause GI adverse effects, like dyspepsia, abdominal pain, and elevated liver enzymes. Cholelithiasis is uncommon. Fibrates may potentiate muscle toxicity when used with statins and potentiate the effects of warfarin.

Nicotinic acid (niacin) is the most effective drug for increasing HDL. It appears to both increase HDL production and inhibit HDL clearance; it also may mobilize cholesterol from macrophages. Niacin also decreases TGs and, in doses of 1500 to 2000 mg/day, reduces LDL-cholesterol.

Niacin produces flushing, pruritus, and nausea; premedication with low-dose aspirin may prevent these adverse effects. Extended-release niacin cause flushing very less often. Most OTC slow-release niacin are not recommended; but the exception is polygel controlled-release niacin.

Niacin can cause liver enzyme elevations and occasionally liver failure, insulin resistance, and hyperuricaemia and gout. It may also increase serum homocysteine levels. In patients with average LDL-cholesterol and below-average HDL-cholesterol levels, niacin combined with statin treatment may be effective in preventing cardiovascular disorders.

Statins can be given to patients with TGs < 500 mg/dL if LDL-cholesterol elevations are also present; statins can reduce both LDL-cholesterol and TGs through reduction of VLDL. Fibrates are the drug of choice only if TGs are elevated.

Omega-3 fatty acids in high doses (1 to 6 g/day of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) can be

effective in reducing TGs. The omega-3 fatty acids EPA and DHA are the active ingredients in marine fish oil or ω-3 capsules. Adverse effect may be eructation and diarrhoea. These may be reduced by giving the fish oil capsules with meals in divided doses. Omega-3 fatty acids can be a useful addition to other therapies.

Treatment for Low HDL

Treatment to increase HDL-cholesterol levels may decrease risk of death, but data are limited. ATPIII guidelines define low HDL-cholesterol as < 40 mg/dL [< 1.04 mmol/L]; the guidelines do not specify an HDL-cholesterol target level and recommend interventions to raise HDL-cholesterol only after LDL-cholesterol targets have been reached. Treatments for LDL-cholesterol and TG reduction often increase HDL-cholesterol, and the 3 objectives can sometimes be achieved simultaneously. No guidelines specifically address treatment of low HDL-cholesterol in children.

Treatment includes lifestyle changes such as an increase in exercise weight loss. Alcohol raises HDL-cholesterol but is not routinely recommended as a therapy because of its many other adverse effects. Drugs are useful when lifestyle changes alone are insufficient.

Nicotinic acid may also be useful

Fibrates increase HDL. Infusion of recombinant HDL (e.g., apoprotein A-1 Milano, an HDL variant in which a cysteine is substituted for an arginine at position 173 allowing for dimer formation) appears promising as a treatment for atherosclerosis but requires further study.

Treatment for Elevated Lp (a)

The upper limit of normal for Lp (a) is about 30 mg/dL (0.8 mmol/L), but values in African-Americans run higher. Few data exist to guide the treatment of elevated Lp (a) or to establish treatment efficacy. Niacin is the only drug that directly decreases Lp (a); it can lower Lp (a) by ≤ 20% at higher doses. The usual approach in patients with elevated Lp (a) is to lower LDL-cholesterol aggressively.

Treatment for Secondary Causes

Treatment of diabetic dyslipidaemia should always involve lifestyle changes, with statins to reduce LDL-cholesterol, fibrates to decrease TGs, or both drugs. Metformin lowers TGs, which may be a reason to choose it over other oral antihyperglycaemic drugs when treating diabetes. Some thiazolidinediones (TZDs) increase both HDL-cholesterol and LDL-cholesterol (probably the less atherogenic large, buoyant type of LDL). Some TZDs also decrease TGs.

These antihyperglycaemic drugs should not be chosen over lipid-lowering drugs to treat lipid abnormalities in diabetic patients but may be useful adjuncts. Patients with very high TG levels and less than optimally controlled diabetes may have better response to insulin than to oral antihyperglycaemic drugs.

Treatment of dyslipidaemia in patients with hypothyroidism, renal disease, liver disease, or a combination of these disorders involves treating the underlying disorders primarily and lipid abnormalities secondarily. Abnormal lipid levels in patients with low-normal thyroid function (high-normal TSH levels) improve with hormone replacement. Reducing the dosage of or stopping drugs that cause lipid abnormalities should be considered.

Other Drug Categories

Anion-exchange Resins[20]

1. Cholestyramine and colestipol act by binding bile acids, preventing their reabsorption. The resultant increased LDL-receptor activity of liver cells increases the clearance of LDL-cholesterol.
2. Both drugs effectively reduce LDL-cholesterol but can aggravate hypertriglyceridaemia.
3. They can be offered as an alternative for primary and secondary prevention to patients where statins are not tolerated or contraindicated.

Plant Sterols and Stanols

NICE do not recommend that these are prescribed routinely for the primary prevention of CVD.[21] Although sterols and stanols have been shown to reduce total cholesterol, further research is required to demonstrate whether this translates into a reduction in CVD.

Monitoring Treatment[22]

Lipid levels should be monitored periodically after starting treatment. No data support specific monitoring intervals, but measuring lipid levels 2 to 3 months after starting or changing therapies, and once or twice yearly after lipid levels are stabilized is common practice.

Despite the low incidence of liver and muscle toxicity with statin use (0.5 to 2% of all users), current recommendations are for baseline measurements of liver and muscle enzyme levels at the beginning of treatment. Many practitioners obtain at least one additional set of liver enzymes 4 to 12 week after beginning treatment and annually thereafter.

Statin therapy can be continued unless liver enzymes increase to > 3 times the upper limit of normal. Muscle enzyme levels checking is not needed regularly unless patients develop myalgias or other muscle symptoms. If muscle damage is suspected, statin use should be stopped and CK can be measured. When symptoms go down, a lower dose or a different statin can be tried.

Notes[23]

1. Combinations of a statin with an anion exchange resin, nicotinic acid or a fibrate carry an increased risk of side-effects (including rhabdomyolysis) and NICE does not recommend them for the primary prevention of CVD.
2. NICE considers that the case for the cost effectiveness (including adverse events) of higher intensity statins (either alone or in combination with other classes of drug) to reduce CVD events by treating to target levels of total cholesterol of either 5 mmol/L or 4 mmol/L (or comparable LDL cholesterol levels) has yet to be proved.

Complications[24]

1. About 46% of deaths due to coronary heart disease (CHD) may be attributable to raised serum cholesterol.
2. People with heterozygous familial hypercholesterolaemia have a four-fold increased risk of CHD.
3. People with familial combined hyperlipidaemia also have an increased risk of CHD, but CHD usually only presents after the age of 60 years.
4. Untreated very severe hypertriglyceridaemia (more than 10 mmol/L) is a risk factor for pancreatitis.
5. Decreased levels of serum HDL cholesterol (HDL-C) are also an independent risk factor for CHD.

Indications for Referral[25]

These include:

1. Suspected familial hypercholesterolaemia: TC greater than 7.5 mmol/L (or LDL-C greater than 4.9 mmol/L) and at least one of the following:
    a. Tendon xanthomata in patient or in a first- or second-degree relative.
    b. Family history of premature CHD.
    c. Family history of TC greater than 7.5 mmol/L.
2. Suspected familial combined hyperlipidaemia[26], i.e. mixed hyperlipidaemia and a family history of hyperlipidaemia or premature CHD.
3. Failure of therapy: failure to meet target lipid reduction despite maximally tolerated therapy.
4. Severe hypercholesterolaemia: initial TC greater than 10 mmol/L.
5. Very severe hypertriglyceridaemia: triglycerides greater than 10 mmol/L.

The Other Side of Statins

Clinical studies and epidemiological analysis established the relationship between high cholesterol level, atherosclerosis, and CVD. Therefore, reducing the level of cholesterol decreases susceptibility to CVD, and in high risk individuals, prolongs life.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors[27] (statins) constitute a new class of cholesterol-lowering drugs. They competitively inhibit the enzyme HMG-CoA reductase, which catalyzes the rate-limiting step in cholesterol biosynthesis, that is, the conversion of HMG-CoA to mevalonate. In the blood, cholesterol circulates attached to low density lipoprotein (LDL) particles, whose

function is to provide cells with cholesterol. The statin-induced inhibition of HMG-CoA reductase is thought to decrease the cellular cholesterol content and thus to stimulate the production of LDL receptors. This, in turn, leads to an increased cellular uptake of circulating LDL particles and ultimately to lower total serum cholesterol and LDL cholesterol levels.

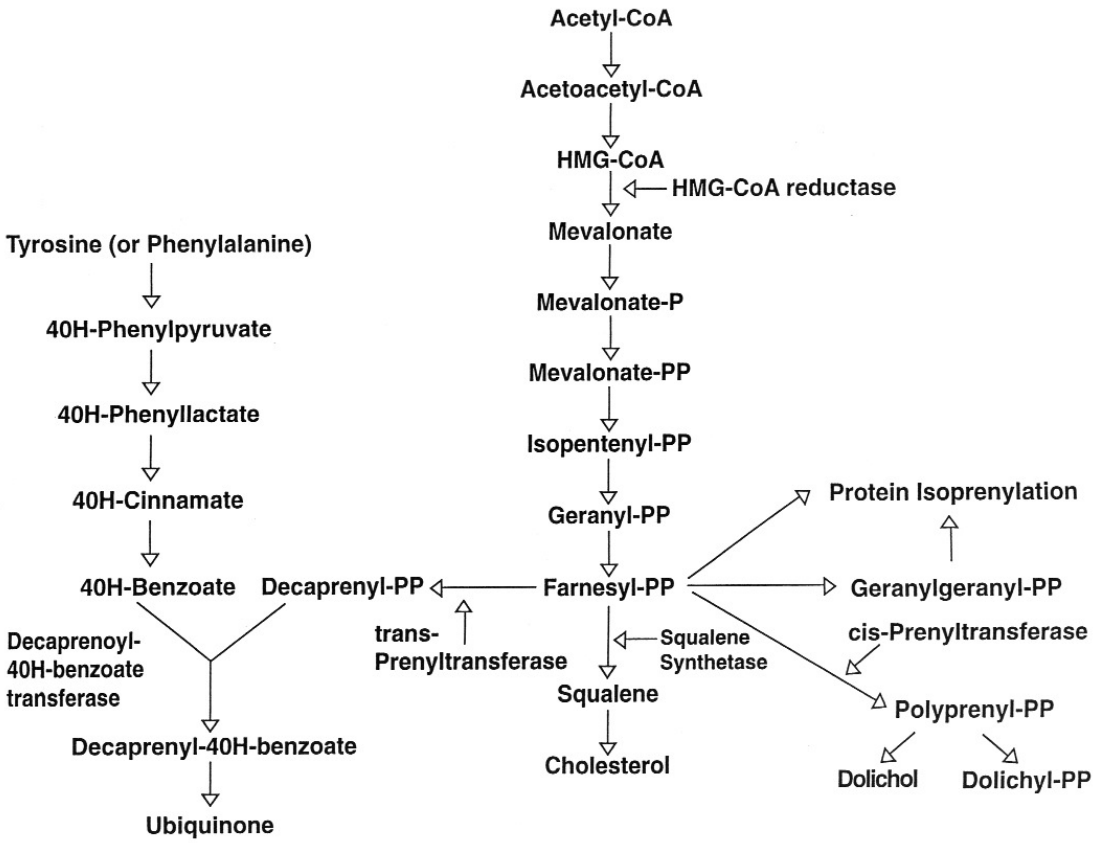
Undermining this advancement is the proverbial "other side of the coin."[28]. Mevalonate is the precursor not only of cholesterol, but also of many nonsteroidal isoprenoid compounds vital to diverse cellular functions, including cell proliferation.Fig.1 shows that.

These isoprenoids include dolichols, required for glycoprotein synthesis and coenzyme Q 10, involved in intracellular electron transport and energy generation. Thus, while inhibition of the mevalonate pathway suppresses cholesterol production; it also reducesCoQ bioavailability, causing CoQ deficiency.

It is now well established that oxidative stress resulting from the formation of intracellular or extracellular free radicals and reactive oxygen species

(ROS) is a major factor in the pathogenesis of CVD. More specifically, oxidized cholesterol has deleterious effects, including carcinogenicity, mutagenicity, and initiation or acceleration of the atherosclerotic process. However, systems undoubtedly exist to protect LDL-cholesterol particles in the blood from oxidative damage. Attention has mostly been directed at fat-soluble antioxidants, such as alpha-tocopherol, beta-carotene and coenzyme Q, which are present in LDL in quantities that can be modified by dietary food intake or oral supplementation. Clearly, the depletion of CoQ by statins is a serious clinical concern, since this depletion can initiate or intensify LDL-cholesterol oxidation.

Fig. 1. Reaction Pathway Of The Biosynthesis Of Cholesterol, Coenzyme Q10 (Ubiquinone)and Dolichols



In his book 'The Antioxidant Miracle', Packer wrote that antioxidants function better in a coordinated manner with one another, which he calls the "antioxidant network". In particular, the interaction of CoQ with vitamin E is critical to the overall antioxidant defence and has important clinical ramifications.

Coenzyme Q10 (Ubiquinone)

Coenzyme Q (coenzyme Q10 or CoQ10 in humans, (2, 3-dimethoxy-5-methyl-6-decaprenyl-1, 4-benzoquinone) is a naturally occurring, fat-soluble nutrient, with characteristics common to vitamins and, like vitamins, is essential for the optimal functioning of an organism. CoQ was discovered in 1957 by Crane and his associates as a component of beef heart mitochondria. In 1958

Folkers and his associates determined its chemical structure. Peter Mitchell was awarded the Nobel Prize in Chemistry in 1978 for his elucidation of the "Q-cycle."

The essential role of CoQ for cellular energy production in eukaryotes is well established. A vital electron and proton carrier, CoQ supports adenosine triphosphate (ATP) synthesis in the mitochondrial inner membrane and stabilizes cell membranes, thus preserving cellular integrity and function. CoQ10 is a potent and versatile antioxidant that blocks oxidative injuries to DNA, lipids, proteins, and other essential molecules. This well-documented function prevents or retards the development of many cardiovascular, neoplastic, and probably neurodegenerative diseases.

Several publications illustrate how, diet-derived antioxidants participate in protection against these diseases. It has been reported that the normal level of CoQ in mitochondrial membranes is below that required for kinetic saturation. This finding strongly indicates that CoQ might be a rate-limiting component in the respiratory chain, especially in the mitochondria of injured Tissues.

The biosynthesis of CoQ is an elaborate 17-step process, first described by Folkers that requires the availability of several vitamins or their coenzyme forms: vitamins B2, B6, B12, C, folic acid, niacinamide, pantothenic acid, as well as many trace elements. Deficiencies of one or more of these building blocks will result in CoQ deficiency, with subsequent impairment of certain vital functions. The clinical manifestations of CoQ deficiency are diverse and are determined by the cells and organs involved. Additionally, an age-dependent decline of CoQl0 level is postulated to be responsible, in part, for the diseases of aging. Bioenergetic degradation resulting from CoQ10 deficiency affects first and most intensely the cardiovascular and immune systems, whose cells and organs place the highest

energy demands of all body systems. Working with suboptimal energy, a cascade of functional impairment begins in these systems, as do overt clinical manifestations. Not surprisingly, cardiovascular and neoplastic diseases are the most common causes of morbidity and mortality in the elderly.

Interest in the use of antioxidants for prevention and treatment of human diseases has been sustained for at least two decades. Developments in both therapeutic and nutritional fields have been punctuated by successes and some failures. It is important to note that in his book on CoQ10, Littarru devoted 71% of the content to the CoQ10 defence against oxidative damage.

In conclusion, CoQ10 is an essential nutritional factor, not a drug. This indisputable fact, unfortunately, hinders its acceptance by most conventional clinicians despite the reported clinical and experimental results.

Dolichols

Proteins, those magic particles so important to our function and destiny, are synthesized within the membranes of the endoplasmic reticulum (ER), a tubular marvel of complexity within each of our cells.[29]

It is within this microscopic structure that amino acids are linked together into a popcorn string-like peptide. Some peptides will ultimately serve for cell identification so they may wander about our immune system without being challenged; others produce insulin because our blood sugar is rising.

This class of proteins contains a signal as a recipe to guide the ER assembly of our necessary peptide, thereby matching our immediate needs. This entire process is orchestrated by dolichols in

the form of dolichol phosphate. In terms of chain of command, it cannot be told who issues the command for a certain peptide, for that is beyond our understanding at this time, but the command once given is carried out by dolichol, the executive officer of this amazing process. We are dealing with a factory producing a substance, assembly-line fashion, under an administration process familiar to any production line facility.This peptide assembly process is greatly disturbed by statin drug use.

During the congregation of the peptide strand within the ER, sugars are added thereby converting the product into glycoproteins. The sugars usually found in glycoproteins are glucose, galactose, mannose, fucose, N-acetyl galactosamine, N-acetyl glucosamine and N-acetyl neuraminic acid. The most recurrently found sugar in this course is mannose. Their role is to broaden the versatility of the evolving protein structure by designating points and direction of protein folding.

The ultimate role depends on the protein structure. Just utilizing proteins can give hundreds of options but the addition of these sugars to the protein strand gives tens of thousands of structural options. It is this almost boundless range of structural options that gives humans our incredible range of behavioral and emotional reactions. This progression, too, is orchestrated by dolichols in its groundwork of the final protein structure.

This dolichol-mediated route is involved in neuropeptide configuration and cell communication, cell identification and immune system functions. This intricate role is such that almost anything can be expected when dolichols are deficient. Altered emotional and behavioral reactions associated with statin use are likely explained by misrepresented neuropeptide formation.

The reality of dolichol inhibition by Statins is certainly documented. The role of dolichols in the process of glycoprotein synthesis is also systematically documented.

Dolichyl Phosphate Phosphatase (dolichyl pp)

Apart from blocking the biosynthesis of coenzyme Q 10 and dolichols, statins also block Dolichyl PP production. In enzymology,[30] dolichyl-phosphatase (EC 3.1.51) is an enzyme that catalyses the chemical reaction.

$$\text{Dolichyl Phosphate} + H_2O \rightleftharpoons \text{Dolichol} + \text{Phosphate}$$

Thus, the two substrates of this enzyme are dolichyl phosphate and H_2O, whereas its two products are dolichol and phosphate.

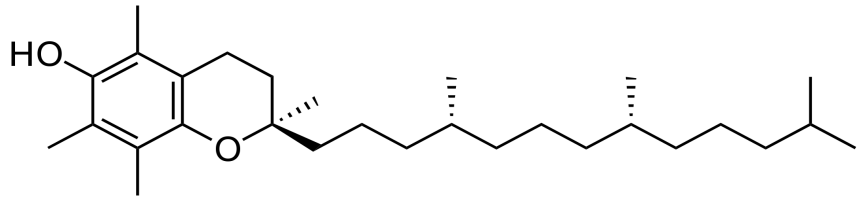
Since statin therapy disturbs the biosynthesis of coenzyme Q10, dolichols, and dolichyl pp these products are to be supplemented along with statin therapy, to cope up with their deficiencies, to ensure normal functioning of the body.

DRUG PROFILE

VITAMIN E[68]

Vitamin E is a generic term for tocopherols and tocotrienols. Vitamin E is a family of α , β, γ, and δ - tocopherols and corresponding four tocotrienols. Vitamin E is a fat-soluble antioxidant that stops the production of reactive oxygen species formed when fat undergoes oxidation. Of these, α-tocopherol has been most studied as it has the highest bioavailability.

Chemically it is (2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]- 3,4-dihydrochromen-6-ol. It is a Light yellow color, odourless substance with the molecular formula $C_{29}H_{50}O_2$. Its Molecular weight is 430.7061 g/mol. The structural formula is represented below:



Sources:

Vitamin E is found in variety of foods including Fortified cereals**,** Green leafy vegetables, Tomato products, Rockfish, Papayas, Seeds, Nuts, Olives, Corn, Asparagus, and Vegetable oils.

Available brands:

Evion (200 mg, 400 mg & 600 mg), E- CAP (200 mg & 400 mg), Ephynal (200 mg & 400 mg), Evitam (200 mg & 400 mg), Evitop (400 mg), Tocofer (200 mg & 400 mg) and Viteolin (200 mg & 400 mg).

Pharmacological classification:

Vitamins & Minerals (Fat – Soluble); Antioxidants.

Indications[69]:

- Alzheimer's Disease
- High blood pressure during pregnancy (pre-eclampsia)
- Premenstrual syndrome (PMS)
- Macular Degeneration
- Cancer Risk Reduction
- In premature infants exposed to high concentration of oxygen
- Vitamin E deficiency
- Nocturnal muscle cramps
- Fibrocystic breast disease
- Coronary artery disease.

Dosage and administration:

Administration:

Usually administered orally; may administer parenterally as a component of a multivitamin injection.

Dosage:

Vitamin E deficiency:

Adult: 40-50 mg/day

Child: Neonate: 10 mg/kg/day; 1 month –18 yr: 2–10 mg/kg/day, up to 20 mg/kg

Supplementation in cystic fibrosis:

Adult: 67-135 mg/day.

Child: As α- tocopheryl acetate: 1 month –1 yr: 50 mg/day; 1–12 yr: 100 mg/day; 12–18 yr: 200 mg once daily. Dose to be adjusted as needed.

Abetalipoproteinaemia:

Adult: 33-67 mg/kg/day.
Child: Neonate: 100 mg/kg/day; 1 mth–18 yr: 50–100 mg/kg/day.

Clinical Pharmacology:

Mechanism of Action

Vitamin E reacts with free radicals and protects RBCs against haemolysis and PUFA's in membranes against free radical attack.

Pharmacodynamics[70]:

Although all forms of Vitamin E exhibit antioxidant activity, it is known that the antioxidant activity of vitamin E is not sufficient to explain the vitamin's biological activity. Vitamin E's anti- atherogenic activity involves the inhibition of the oxidation of LDL and the accumulation of oxLDL (Oxidized LDL) in the arterial wall. It also appears to reduce oxLDL-induced apoptosis in human endothelial cells. Oxidation of LDL is a key early step in atherogenesis as it triggers a number of events which lead to the formation of atherosclerotic plaque. In addition, vitamin E inhibits Protein Kinase C (PKC) activity. PKC plays a role in smooth muscle cell proliferation, and, thus, the inhibition of PKC results in inhibition of smooth muscle cell proliferation, which is involved in atherogenesis. Vitamin E's antithrombotic and anticoagulant activities involves the downregulation of the expression of Intracellular Cell Adhesion Molecule (ICAM)-1 and Vascular Cell Adhesion Molecule (VCAM)-1 which lowers the adhesion of blood components to the endothelium.

Pharmacokinetics:

Absorption

20-80% absorbed from gastrointestinal tract. Absorption depends on the presence of bile and on normal pancreatic function; decrease with increasing dose.

Distribution

Readily distributed into all tissues and stored in adipose tissue. Crosses the placenta. Distributed into human milk.

Metabolism

Extensively metabolized in the liver, to glucuronides of tocopheronic acid and its γ-lactone.

Excretion

Excreted principally in the feces via biliary excretion; also excreted in urine.

Cautions:

Abdominal pain**,** blurred vision, breast enlargement**,** dizziness, diarrhea**,** influenza-like symptoms, headache**,** nausea, tiredness**,** weakness.

Mortality

Long-term administration (>1 year) of high doses of vitamin E (≥400 units daily) may increase all-cause mortality.

Specific Populations:

Pregnancy

Category A.

Lactation

Distributed into human milk.

Adverse drug reactions:

Hypertension, thrombophloebitis, myopathy, nausea, diarrhoea, abdominal pain, Intestinal cramping, Fatigue, weakness, headache, dizziness, Blurred vision, Any unusual bruising or bleeding, Signs of gastrointestinal bleeding. Topical: Contact dermatitis.

Drug interactions:

Anticoagulants:

Risk of hemorrhage with large doses of vitamin E.

Iron supplements:

Vitamin E dosages ≥10 units/kg daily may delay response to iron therapy in children.

Mineral oil:

Possible impaired absorption of vitamin E.

Orlistat:

Possible impaired absorption of vitamin E.

Others:

Drugs such as antacids, Cholestyramine, Colestipol may decreases the absorption of Vitamin E.

Storage:

Do not freeze. Store in a cool, dry place away from direct light.

COENZYME Q 10

Other Names: CoQ10, Q 10, Ubiquinone, Ubiquinol 10, Ubidecarenone, Vitamin Q 10.[71]

Class: Vitamin-like nutrient, heart energizer, strong antioxidant

Dose: 30 mg -300 mg/day[72]

Route of Administration: Oral and I.V.

Mechanism of Action:

CoQ10 is a fat-soluble substance and therefore it is absorbed like any other fat in our diet. Digestion releases dietary CoQ10 from the food matrix. CoQ10 supplements that are based on pure CoQ10 may not require gastric digestion.In the small intestine, secretions from the pancreas and bile enables emulsification and micelle formation that are inevitable for the absorption of fats along the small intestine. No “active” transport mechanism is there for the absorption of fats. Once CoQ10 is absorbed by the intestinal mucosal cells, it is transported through the lymphatic system as part of the chylomicrons and eventually taken up by the liver for repackaging into lipoprotein particles and rereleased into the circulation.[73]

CoQ10 is present in all tissues in our body. In blood it is linked with lipoproteins. The concentrations fluctuate from tissue to tissue. Heart, muscle, liver, kidney and brain which are with high rates of metabolic activity and high energy demands contain relatively high concentrations of CoQ10. The state of CoQ10 (oxidized vs. reduced, i.e. ubiquinone vs. ubiquinol) also varies from tissue to tissue, and tissues with high aerobic activity generally contain higher amounts of the oxidized form. In circulation, CoQ10 is present predominantly as ubiquinol). The ratio of oxidized to the reduced form in blood is related

to oxidative stress. Recent studies shows that the level of circulating CoQ10 tends to decline in certain disease conditions, such as diabetes, liver disease, down syndrome, etc.

Coenzyme Q 10 is a fat-soluble substance. It is well absorbed when taken along with fatty diet. So it was given in the form of soft gelatin capsules filled with olive oil or soy bean oil in which Coenzyme Q 10 was dissolved.

Indications

Cardiovascular disease : Cardiomyopathy, Congestive heart failure, Angina pectoris,Arrhythmias, Mitral valve prolapse, Hypertension, Atherosclerosis, Cardiotoxicity (drug induced)

Neurodegenerative diseases: Huntington's Disease, Parkinson's Disease, Alzheimer's Disease, Amyotrophic lateral sclerosis (Lou Gehrig's Disease).

Neuromuscular diseases: Mitochondrial cytopathies (MELAS, MERRF, etc.) and Muscular dystrophy, Ataxias, Diabetes, Cancer, Chronic obstructive pulmonary disease, Asthma, Migraine, Immune disorders, HIV/AIDS, Periodontal disease, Chronic fatigue syndrome and Male infertility.[71]

Drug Interactions

If you are currently being treated with any of the following medications, you should not use CoQ10 without first talking to your health care provider.

Daunorubicin and doxorubicin[72] - Coenzyme Q10 may help to reduce the toxic effects on the heart caused by daunorubicin and doxorubicin, two chemotherapy medications that are commonly used

to treat several kinds of cancer. Get your oncologist advice before taking antioxidants along with chemotherapy.

Blood pressure medications - In a clinical study of individuals taking blood pressure medications, including diltiazem, metoprolol, enalapril, and nitroglycerin.CoQ10 supplementation to the individuals made them to take lower dosages of these drugs. As per this study, CoQ10 may enhance the effectiveness of certain blood pressure medications, but more research is needed to verify these results.

Blood-thinning medications - CoQ10 chemically resembles vitamin K. Since vitamin K counters the anticoagulant effects of warfarin (Coumadin), it is said that CoQ10 may have the same effect. But, a small, double-blind study found no interaction between CoQ_{10} and warfarin.There have been reports that coenzyme Q10 may decrease the effectiveness of blood-thinning medications such as warfarin or clopidigrel, leading to the need for increased doses. Therefore, this medication must be monitored very closely for maintenance of appropriate levels and steady blood thinning. CoQ10 should be used with warfarin only under careful medical supervision.

Timolol - CoQ10 supplementation may reduce the heart-related side effects of timolol drops, a beta-blocker medication used to treat glaucoma, without decreasing the effectiveness of the medication.

Other - Medications that can lower the levels of coenzyme Q10 in the body include statins for cholesterol , including atorvastatin, lovastatin, pravastatin, and simvastatin, fibric acid derivatives for cholesterol, including gemfibrozil, beta-blockers for high blood pressure, such as atenolol, labetolol, metoprolol, and propranolol, and tricyclic antidepressant medications, including amitriptyline, doxepin, and imipramine.

Nutrient Interactions

Coenzyme Q 10 plays a critical role in maintaining our supply of vitamin E. When vitamin E gets "used up", coenzyme Q 10 can "recharge" it, and restore its antioxidant capability.[73]

Contra-indications

Pregnancy, lactation, young children, patients with severe liver or kidney disease.

Side Effects:

In general, CoQ 10 appears to be extremely safe. No significant side effects have been found, even in year long studies. The side effect reported is mild transient nausea. No toxicity has been found, even at high doses, in animals or humans. No serious side effects have been reported from the use of coenzyme Q10.[74] Some patients using coenzyme Q10 have experienced mild insomnia (inability to sleep), elevated levels of liver enzymes, rashes, nausea, and upper abdominal pain. Other reported side effects have included dizziness, visual sensitivity to light, irritability, headache, heartburn, and fatigue.

ATORVASTATIN

Class: HMG-CoA Reductase Inhibitors

Mechanism of Action:

Atorvastatin is an oral drug that lowers the level of cholesterol in the blood. It belongs to a class of drugs referred to as statins, which includes lovastatin, simvastatin, fluvastatin, and pravastatin. All statins, including atorvastatin, prevent the production of cholesterol in the liver by blocking HMG-CoA reductase, an enzyme that makes cholesterol. Statins reduce total cholesterol as well as LDL cholesterol in blood. LDL cholesterol is believed to be the "bad" cholesterol that is primarily responsible for the development of coronary artery disease.[61] Reducing LDL cholesterol levels retards progression and may even reverse coronary artery disease. Atorvastatin also reduces the level of triglycerides in the blood and raises the level of HDL ("good") cholesterol. High blood concentrations of triglycerides is always associated with coronary artery disease. Atorvastatin was approved by the FDA in December 1996.

Dose:

Atorvastatin is prescribed once daily. The usual beginning dose is 10 to 20 mg per day, and the maximum dose is 80 mg per day. Individuals who need more than a 45% reduction in LDL cholesterol may be started at 40 mg daily.[74] Atorvastatin may be taken with or without food and at any time of day.

Route of Administration: Oral

Indications: Hyperlipidaemia, hypertriglyceridaemia, hypercholesterolaemia.

Drug Interactions:

Reduced elimination of atorvastatin could raise the levels of atorvastatin in the body and hike up the risk of muscle toxicity from atorvastatin. So, atorvastatin should not be given with drugs that lowers its elimination. Examples of such drugs include erythromycin, ketoconazole, itraconazole, clarithromycin, telithromycin, cyclosporine, nefazodone, and HIV protease inhibitors such as indinavir and ritonavir.[75]

Use caution if the following drugs are combined with atorvastatin because serious side effects such as muscle injury (myopathy) infrequently could occur: Fibrates (e.g., Gemfibrozil, Fenofibrate, e.t.c.), high-dose Niacin (1 gram or more per day). Before using this medication, tell your doctor or pharmacist of all prescription and nonprescription/herbal products you may use, especially of birth control pills, cholestyramine, clopidogrel, colestipol, digoxin, HIV protease inhibitors (e.g., indinavir, ritonavir), other drugs which affect certain liver enzymes (CYP 3A4 substrates, inhibitors, and inducers such as amiodarone, cyclosporine, diltiazem, verapamil, rifampin, St. John's wort, carbamazepine).

All Labeled Uses

Arteriosclerotic vascular disease, heterozygous hypercholesterolemia, homozygous familial hypercholesterolemia, hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, myocardial infarction prevention, prevention of cerebrovascular accident, primary dysbetalipoproteinemia, primary prevention of coronary heart disease, and slow progression of coronary artery disease[76]

Unlabeled Uses

Prevention of transient ischaemic attack.

Side Effects

Atorvastatin is usually well-tolerated. Minor side effects like constipation, diarrhoea, fatigue, gas, heartburn, and headache are known to occur. Atorvastatin may cause liver and muscle damage. Serious liver damage caused by statins is uncommon.

More frequently, statins cause abnormalities of liver tests, and, so, periodic measurement of liver tests in the blood is recommended for all statins. Abnormal tests generally come back to normal even if a statin is continued, but if the abnormal test value is higher than three times the upper limit of normal, the statin generally is stopped. Liver tests should be done before initiation, at 12 weeks following initiation of therapy and dose changes, and periodically thereafter.

Inflammation of the muscles caused by statins can lead to serious breakdown of muscle cells called rhabdomyolysis. Rhabdomyolysis causes the release of muscle protein (myoglobin) into the blood, and myoglobin can cause kidney failure and even death. When given alone, statins cause rhabdomyolysis in less than one percent of patients. To prevent the development of serious rhabdomyolysis, patients taking atorvastatin should contact their healthcare provider immediately if they develop unexplained muscle pain, weakness, or muscle tenderness.

Adverse Effects

Most Frequent:

Abdominal Pain with Cramps, Constipation, Dyspepsia, Flatulence

Less Frequent:

Allergic Reactions, Arthralgia, Diarrhoea, Dizziness, Flu-Like Symptoms, Headache Disorder, Nausea, Pain, Pharyngitis, Sinusitis, Skin Rash.

Rare:

Abnormal Hepatic Function Tests, Alopecia, Amblyopia, Anaphylaxis, Anaemia, Angina, Anorexia, Arthritis, Bronchitis, Bursitis, Chest Pain, Colitis, Conduction Disorder of the Heart, Contact Dermatitis, Cramps in Legs, Cystitis, Drowsy, Dry Eye, Dysgeusia, Dyspnoea, Ecchymosis, Epididymitis, Erythema Multiforme, oesophagitis, Fainting, Fatigue, Fever, Fibrocystic Breast Disease, Gastroenteritis, Gastrointestinal Ulcer, General Weakness, Gingival Bleeding, Glaucoma, Gout, Gynaecomastia, Haematuria, Hepatic Failure, Hepatitis, Hyperglycaemia, Hyperhidrosis, Hypertonia, Hypoglycaemic Disorder, Increased Urinary Frequency, Insomnia, Kidney Stone, Libido Changes, Lymphadenopathy, Memory Impairment, Metrorrhagia, Myalgia, Myopathy, Neck Stiffness, Ocular Bleeding, Orthostatic Hypotension, Palpitations, Pancreatitis, Paraesthesia, Peripheral oedema, Peripheral Neuropathy, Proteinuria, Pruritus of Skin, Rectal Bleeding, Rhabdomyolysis, Rhinitis, Skin Photosensitivity, Stevens-Johnson Syndrome, Stomatitis, Tendon Rupture, Thrombocytopaenic Disorder, Tinnitus, Toxic Epidermal Necrolysis, Urinary Tract Infections, Vomiting, Xerostomia

Contraindications

Most Significant

Abnormal Hepatic Function Tests, Disease of Liver, Hepatic Failure, Lactating Mother, Pregnancy, Rhabdomyolysis.

Significant

Alcoholism, Myopathy with CK Elevation, Severe Hypotension, Severe Infection, Surgical Procedure, Trauma, Uncontrolled Epilepsy.

Possibly Significant

Haemorrhagic Stroke, Myalgia, Renal Disease, Transient Cerebral Ischaemia, Untreated Hypothyroidism.

Warnings

Pediatric

1. Safety and efficacy under 10 years of age and in pre-menarche girls are not established.
2. Post-menarche females should be counseled on appropriate contraception.

Lactation: Absolute Contraindication

Pregnancy: Absolute Contraindication

Geriatric

Precaution: Myopathy, Rhabdomyolysis and Liver dysfunction.

LITERATURE REVIEW

- **Giuseppe Caso**[31] and his colleagues performed a preliminary study on the effect of coenzyme Q 10 on statin induced myalgia. Patients with myopathic symptoms were randomly assigned in a double-blinded protocol to treatment with coenzyme Q10 (100 mg/day, n _ 18) or vitamin E (400 IU/day, n _ 14) for 30 days. Muscle pain and pain interference with daily activities were assessed before and after treatment. After a 30-day intervention, pain severity decreased by 40% (p <0.001) and pain interference with daily activities decreased by 38% (p <0.02) in the group treated with coenzyme Q10. In contrast, no changes in pain severity (_9%, p _ NS) or pain interference with daily activities (_11%, p _ NS) was observed in the group treated with vitamin E. They concluded that coenzyme Q10 supplementation may decrease muscle pain associated with statin treatment and so coenzyme Q10 supplementation may offer an alternative to stopping treatment with these vital drugs.

- **Gazdikova-et-al**[32], studied the effect of coenzyme Q 10 in patients with kidney disease. The study involved 15 patients in which 5 had tubulopathy and 10 had chronic tubulointerstitial nephritis. All the 15 patients received antioxidant therapy for 3 months with vitamin E, vitamin C, and riboflavin. And for the last 2 months coenzyme Q 10 was added. At the end of the study tests for renal functions, lipid spectrum, lipid peroxidation parameters (malondialdehyde), and levels of alpha-tocopherol, beta-carotene and coenzyme Q 10 were performed. Coenzyme Q10 levels significantly increased (p < 0.001) to the values of 1.66 +/- 0.16 mumol/l in blood and to 1.78 +/- 0.27 mumol/l in plasma. Plasma levels of beta-carotene increased from the markedly subnormal values 0.25 +/- 0.07 mumol/l (rr > 0.8 mumol/l) to 0.56 +/- 0.02 mumol/l (no statistical

difference). Plasma levels of alpha-tocopherol remained within the reference range 32.15 +/- 4.73 mumol/l (rr 15-30 mumol/l) and they increased up to the plasma level of 44.83 +/- 5.82 mumol/l during the period of testing. Malondialdehyde levels did not show a significant change within the testing period. No deflections in renal functions and parameters of lipid metabolism were noticed. Patients tolerated the treatment effectively and no adverse effects were seen during the period of observation.Gazdikova concluded that levels of antioxidant CoQ10 were lower in patients with nephropathy who underwent conservative treatment with peroral substation. Such shortage can be amended by CoQ10 administration, which could be therefore taken as complementary treatment of nephrology.

- **Kazuki Nukui**[33] and his coworkers studied the blood Co Q 10 levels after single dose or chronic administration of Water-soluble type Co Q 10(puresorb-QTM 40). Single administration revealed a higher absorption level for P40, taken in the fasting state or together with meals. In this double-blind, placebo controlled, comparative study conducted on 46 healthy volunteers are randomly divided into two groups. The study group received 900 mg of P40 for 4 weeks. The absorption of P40 was very high which was revealed by the the plasma Co Q 10 levels at the end of the 4 weeks. P40 intake did not show any significant deviations in symptoms and clinical laboratory tests as assessed by physical, hematological, blood biochemical or urinalysis. Clinical examinations also did not disclose any abnormalities.

- **Flint Beal**[34] and his colleagues studied the effect of coenzyme Q 10 on the striatal lesions produced by the mitochondrial toxin, malonate. At the end of the one week study the lesions were reduced in size and it was proved with the MRI in vivo. Finally,

they suggested that the coenzyme Q 10 work by blocking the ATP depletions and lactate increases.

- **Munkholm-et-al**[35], Studied, by an invasive method, the effect of Coenzyme Q 10 on serious heart failure.22 patients with mean left ventricular (LV) ejection fraction 26%, mean LV internal diameter 71mm, and in NYHA class 2-3.The patients were given coenzyme Q 10 100 mg twice daily or placebo for 12 weeks in a randomized double-blinded placebo controlled investigation. Before and after the treatment period, a right heart catheterization was done including a 3 minute exercise test. At the end of the 12 weeks study the stroke index at rest and work improved significantly, the pulmonary artery pressure at rest and work decreased (significantly at rest), and the pulmonary capillary wedge pressure at rest and work decreased (significantly at 1 min work),which imply improvement in LV performance. Finally they concluded Patients with congestive heart failure may thus benefit from adjunctive treatment with coenzyme Q10.

- **Rosenfeldt-et-al**[36], performed a meta- analysis on the antihypertensive effect of coenzyme Q 10 and found that some trials documented statistically significant reductions in diastolic or systolic blood pressure or both, while others reported negligible effects. In one small trial, blood pressures actually went up in patients taking coenzyme Q10. Coenzyme Q10 doses and duration of therapy varied from study to study in the meta-analysis. Minor adverse effects such as GI upset and headache were reported.

- **Yamagami**[37] **et al**, studied the antihypertensive effect of coenzyme Q 10.They randomly assigned 20 patients with hypertension and a low coenzyme Q10 level to receive 100 mg of

coenzyme Q10 or placebo daily for 12 weeks. Patients followed their usual antihypertensive regimen during the study period. Blood pressures, coenzyme Q10 levels, and antihypertensive drugs given were comparable between the two study groups. After 12 weeks of therapy, the mean coenzyme Q10 level in the active-treatment group had more than doubled, from 0.704 to 1.597 µg/mL.This group also showed a statistically significant drop in systolic blood pressure, from 167 mm Hg at baseline to 148 mm Hg at 12 weeks. In the placebo group, the systolic blood pressure dropped from 168 mm Hg at baseline to 164 mm Hg at 12 weeks, but the change was not statistically significant. Diastolic pressure also did not go down significantly.. The authors concluded that coenzyme Q10 supplementation induced a mild reduction in high blood pressure in patients who had low coenzyme Q10 serum levels.

- **Digiesi et al**[38], randomized 18 patients with essential hypertension to receive either coenzyme Q10 100 mg or placebo daily for 10 weeks. All antihypertensive therapy was withdrawn at baseline. After the first 10 weeks, patients went through a 2-week washout period and then were given an opposite therapy for an additional 10 weeks. Mean baseline blood pressure was 167/103 mm Hg. Those taking the supplement had a statistically significant decrease in systolic and diastolic pressures ($P < 0.001$). The drop in blood pressure was noted in the 3rd or 4th week of active treatment and persisted for the duration of therapy. The effects debauched 7 to 10 days after coenzyme Q10 was stopped.

- **Langsjoen**[39] **et al**, evaluated the effects of adding coenzyme Q10 to the antihypertensive drug regimen of 109 patients who had a primary diagnosis of essential hypertension in a prospective observational study. Patients having hypertension as a

secondary diagnosis and other cardiovascular diseases were not enrolled. Variable doses of coenzyme Q10 were given, adjusted according to clinical response and to achieve serum levels greater than 2.0 µg/mL. The average dose was 225 mg/day; the mean serum level attained was 3.02 µg/mL. Over several months, patients taking the supplement had a reduction in mean systolic pressure from 159 mm Hg at baseline to 147 mm Hg ($P < 0.001$). A drop in mean diastolic pressure from 94 to 85 mm Hg ($P < .001$) was noticed. Thirty-seven percent of patients were able to discontinue one antihypertensive drug, 11% discontinued two drugs, and 4% were able to stop taking three drugs. However, 46% remained on the same antihypertensive regimen, and 3% needed an additional drug.

- **Singh-et-al**[40], randomized 64 patients who had coronary artery disease and who had been on antihypertensive drugs for more than 1 year to receive either B-complex vitamins or coenzyme Q10 (hydrosoluble Q-Gel) 60 mg orally once daily for 8 weeks. 5 patients were not available for proceedings, so, only 59 patients were monitored. Fifty-five (93%) of the 59 patients were taking only one antihypertensive drug. Initial antihypertensive drug use was similar between study groups and was continued throughout the trial. After 8 weeks of therapy, the coenzyme Q10 group had significantly lower systolic and diastolic blood pressure than the placebo group ($P < 0.05$ for both). There was also a statistically significant decrease in the dosage of antihypertensive drugs in the coenzyme Q10 group but not in the placebo group ($P < 0.05$), reflecting coenzyme Q10's additive antihypertensive effect.

- **Burke**[41], randomized 41 men and 35 women with isolated systolic hypertension (systolic pressure 150–170 mm Hg,

diastolic pressure < 90 mm Hg) to receive a twice-daily dose of 60 mg of emulsified coenzyme Q10 (hydrosoluble Q-Gel) with 150 IU of vitamin E or placebo containing vitamin E alone for 12 weeks. The study also included 5 men and 4 women with normal blood pressure, all of whom received coenzyme Q10. A total of 80 patients completed treatment. The primary goal of the study was to determine the efficacy of coenzyme Q10 in the treatment of isolated systolic hypertension in patients without comorbid conditions. Blood pressures were monitored twice a week during the trial, by the same nurse. After 12 weeks of treatment, the mean reduction in systolic pressure in hypertensive patients on coenzyme Q10 was 17.8 ± 7.3 mm Hg. There were no significant changes in diastolic pressure in any study group with treatment. Patients with isolated systolic hypertension who were taking coenzyme Q10 had a statistically significant reduction in systolic pressure compared with baseline and placebo ($P < 0.01$ for both). Approximately 55% of patients on coenzyme Q10 achieved a reduction in systolic pressure of 4 mm Hg or greater, while 45% did not respond to therapy. The mean plasma coenzyme Q10 level of the treatment group increased from 0.47 ± 0.19 µg/mL to 2.69 ± 0.54 µg/mL after 12 weeks; however, the study did not have the statistical power to demonstrate a relationship between coenzyme Q10 levels and changes in blood pressure. Twenty-seven (34%) of the 80 patients were taking a statin while on coenzyme Q10 therapy.

- **Thibault et-al**[42], reported that patients taking lovastatin (Mevacor) at dosages as high as 35 mg/kg/day to inhibit tumor growth achieved symptomatic relief of statin-induced musculoskeletal toxicity after coenzyme Q10 supplementation.

- **Young et-al**[43] studied the effect of coenzyme Q 10 on stating induced myopathy. They randomized 44 patients with prior statin-induced myalgia to receive increasing doses of simvastatin (10–40 mg/ day) in combination with either coenzyme Q10 (Q-Gel) 200 mg/day or placebo. The primary goal was to determine if coenzyme Q10 supplementation would help improve statin tolerance in patients with a history of statininduced myalgia. Plasma coenzyme Q10 and lipid levels were measured at baseline and at the end of the study. The intensity of myalgia was assessed with a visual analogue scale. At 12 weeks, the coenzyme Q10 plasma level was significantly higher in the treatment group than in the placebo group (P < 0.001). However, no differences were noted between groups in the number of patients who tolerated the 40-mg/day simvastatin dose (P = 0.34) or in the number of patients who remained on any simvastatin dose (P =0 .47). Additionally, myalgia scores did not differ between groups (P = 0.63). The authors acknowledged that there were only small increases in the myalgia pain scores reported in either group. Therefore, patients in the treatment group may not have experienced sufficiently severe muscle pain to have benefited from coenzyme Q10 supplementation.

- **Folkers**[44], studied the effect of coenzyme Q 10 on the Immune function. In the study which included eight chronically ill patients, administration of 60 mg/day of CoQ10 were associated with significant increases in serum levels of immunoglobulin G (IgG) after 27- 98 days of treatment. These studies suggest that CoQ10 may help prevent or reverse the immunosuppression that is associated with aging or chronic disease.

- **Folkers-et-al**[45], studied the effect of coenzyme Q 10 in AIDS patients, in the blood levels of CoQ10 were significantly lower in

patients with AIDS related complex (ARC) than in a control group, and were significantly lower in patients with AIDS than in those with ARC. Six patients with AIDS or ARC were treated with 200 mg/ day of CoQ10. T-cell helper/suppressor ratios increased in three patients, becoming normal in one case. Five patients reported symptomatic improvement, which was dramatic in some cases. Furthermore, none of the patients developed opportunistic infections during a 4-7 month follow-up period. This study demonstrates that CoQ10 deficiency is common in patients with HIV infection, and that supplementation with CoQ10 may improve immune function and reduce the incidence of opportunistic infections.

- **Lockwood et-al**[46], studied the effect of coenzyme Q 10 in Breast cancer patients In the study, 32 women with breast cancer who were classified as "high risk" because of tumour spread to the axillary lymph nodes received daily 90 mg of CoQ10, along with vitamin C, vitamin E, beta-carotene, and essential fatty acids. In six of these cases, the tumour became smaller. During the 18-month treatment period, none of the patients died (the expected number of deaths was four), and none showed signs of further distant metastases. Six patients had an apparent partial remission. In addition, patients receiving CoQ10 required fewer pain killers. In 1995, he performed another study. Two women with metastatic breast cancer received 390 mg/day of CoQ10. One of the patients was a 44- year-old woman with numerous liver metastases. After treatment with CoQ10 for 11 months, all of the liver metastases had disappeared and the patient was reported to be in excellent health. The other patient was a 49-year-old woman with breast cancer that had metastasized to the pleural cavity. After six months of CoQ10 therapy, the pleural fluid had completely resolved and the patient was reported to be in excellent health.

Considering that CoQ10 is virtually free of side effects, empirical treatment of breast cancer with CoQ10 seems justified.

- **Wilkinson et-al**[47], studied the effect of coenzyme Q 10 on periodontal disease. In that open trial, administration of CoQ10 produced "extraordinary post-surgical healing" (2-3 times as fast as usual) in 7 patients with advanced periodontal disease. In1976, he did another study in which eighteen patients with periodontal disease received either 50 mg/day of CoQ10 or a placebo in a 3-week, double-blind trial. Results were assessed according to a "periodontal score," which included gingival-pocket depth, swelling, bleeding, redness, pain, exudates, and looseness of teeth. All eight patients receiving CoQ10 improved, compared to only three of ten receiving the placebo ($p < 0.01$).

- **Van Gaal**[48], studied the effect of coenzyme Q 10 on Obesity. The serum levels of CoQ10 were found to be low in 14 (52%) of 27 morbidly obese patients. Nine of these 27 individuals (five with low CoQ10 levels) received 100 mg/day of CoQ10 along with a 650 kcal/day diet. After 8-9 weeks, the mean weight loss in the CoQ10- deficient group was 13.5 kg, compared with 5.8 kg in those with normal levels of CoQ10.

- **Vanfraecchem et-al**[49], studied the effect of coenzyme Q 10 on Physical performance. In the study, six healthy, sedentary men (mean age, 21.5 years) performed a bicycle ergometer test before and after taking CoQ10 (60 mg/day) for 4-8 weeks. CoQ10 treatment improved certain performance parameters, including work capacity at submaximal heart rate, maximal work load, maximal oxygen consumption, and oxygen transport. These improvements ranged from 3-12% and were evident after about four weeks of supplementation. This study suggests that

administration of CoQ10 improves physical performance in sedentary individuals

- **Folkers et-al**[50], studied the effect of coenzyme Q 10 on Muscular dystrophy, in the double-blind study, 100 mg of CoQ10 was given daily for three months to 12 patients with progressive muscular dystrophy. CoQ10 treatment resulted in significant improvements in cardiac output and stroke volume, as well as increased physical well being in four of eight patients. Subjective improvements included increased exercise tolerance, reduced leg pain, better control of leg function, and less fatigue. The mechanism of action of CoQ10 is probably related to improved energy production in muscle cells.

- **Rozenet-al**[51], studied the Migraine preventive effect of coenzyme Q 10. 32 patients (26 women, 6 men) with a history of episodic migraine with or without aura were treated with 150 mg of coenzyme Q10 per day. 31 of 32 patients completed the study; 61.3% of patients had a greater than 50% reduction in number of days with migraine headache. The average number of days with migraine during the baseline period was 7.34 and this decreased to 2.95 after 3 months of therapy, which was a statistically significant response ($P < 0.0001$). Mean reduction in migraine frequency after 1 month of treatment was 13.1% and further, this increased to 55.3% at the end of 3 months. Mean migraine attack frequency was 4.85 during the baseline period and this decreased to 2.81 attacks by the end of the study period, which was a statistically significant response ($P < 0.001$). There were no side-effects noted with coenzyme Q10. From this open label investigation coenzyme Q10 appears to be a good migraine preventive.

- **Teranet-al**[52], studied the effect of coenzyme Q 10 in pregnant women. This was the first study on pregnant women supplemented with coenzyme Q10. Supplementation of Coenzyme Q 10 began at 20 weeks of pregnancy, and the dose was 200 mg/day. It was able to significantly reduce the incidence of pre-eclampsia, a common disorder of human pregnancy in which the normal haemodynamic response to pregnancy is impaired. This is a leading cause of maternal morbidity and mortality and a significant increase in perinatal mortality.

- **Safarinejad**[53] studied the effect of coenzyme Q 10 on semen parameters, sperm function and reproductive hormones in infertile men. In this study 212 infertile men were treated with 300 mg/day CoQ10 or placebo for 26 weeks.They were having idiopathic oligoasthenoteratospermia. In the CoQ10 group,sperm count and motility values showed a significant improvement. Serum FSH and LH decreased significantly at the 26 week treatment phase. As the serum FSH was low, spermatogenesis was considered to have improved. Moreover Inhibin B, which reflects Sertoli's cell function, increased in the CoQ10 group.

- **Kocharianet-al**[54], studied the effect of coenzyme Q 10 on diastolic function in children with idiopathic dilated cardiomyopathy This is one of the few papers where CoQ10 was given, (from 2 to 10 mg/kg/day, for 6 months) in a double blind trial, to a group of children affected by idiopathic dilated cardiomyopathy. Index of heart failure showed a significant improvement. Myocardial performance index also showed a significant improvement.

- **Hamilton**[55] studied the effect of coenzyme Q 10 on endothelial dysfunction in statin-treated type 2 diabetic patients This study is consistent with previous reports on the vascular effects of CoQ10. There was a significant increase Flow Mediated Dilation (FMD) in type 2 diabetic patients on stable statin therapy, who received 200 mg CoQ10/day for 12 weeks.

- **Kenji-et-al**[56] of Japan studied the safety profile of coenzyme Q 10(Kaneka Q 10).It was double-blind, randomized, placebo-controlled study. Coenzyme Q10 in capsule form was taken for 4 weeks at doses of 300, 600, and 900 mg/day by a total of 88 adult volunteers. No serious ADRs were observed in any group. But were reported in 16 with placebo, in 12 with the 300 mg , in 20 with the 600 mg, and in 16 volunteers with the 900 mg dose. Common cold symptoms and gastrointestinal effects such as abdominal pain and soft faeces were reported. Changes seen in blood data and biochemical data showed that Kaneka Q10 was well-tolerated and safe for healthy adults till a dose of 900 mg.

- **Yeutsu Ihara et-al**[57] studied the effect of coenzyme Q 10 mitochondrial encephalomyopathy (MELAS). Two patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes (MELAS) in one family are reported. Pathological examination of case 1 showed ragged-red fibers, with 7% of the fibers being unstained by cytochrome c oxidase stain, peripheral nerve damage, multiple areas of softening in the cerebrum and midbrain, and spongy changes in the cerebrum, optic nerve and pons. Electron microscopic examination showed abnormal accumulations of mitochondria in the skeletal, smooth and cardiac muscle. The effect of cytochrome c oxidase on the brain and liver showed a decrease. In a maternal aunt of case 1, with coenzyme Q10, muscular weakness and peripheral nerve damage improved.

- **Soja et-al**[58], studied the effect of coenzyme Q 10 on congestive heart failure. Meta-analysis was performed.. The parameters ,measured were stroke volume (SV), cardiac output (CO), ejection fraction (EF), cardiac index (CI), end diastolic volume index (EDVI), systolic time intervals (PEP/LVET) and total work capacity (W_{max}). The supplemental treatment of CHF with CoQ10 is consistent with an improvement of SV, EF, CO, CI and EDVI. Homogeneity was established for SV and CO.

- **Dr. Shultz**[59], conducted a pilot study on the effect of coenzyme Q 10 on patients with Parkinson's disease, which showed that consumption of up to 800 mg/day of coenzyme Q10 was well-tolerated and significantly increased the level of coenzyme Q10 in the blood. The group that received the largest dose of coenzyme Q10 (1,200 mg/day) showed 44 percent less decline in mental function, ability to carry out activities of daily living, such as feeding or dressing themselves and motor (movement) function. Daily activities improved. Significant increase in energy-producing reactions within their mitochondria was observed in the groups that received coenzyme Q10. The authors concluded that a dose up to 1200mg/day is safe and more effective than lower doses.

- **Gaby-et-al**[60], studied the effect of coenzyme Q 10 on melanoma. In this Non-randomized trial was performed.400 mg of Coenzyme Q 10 was given per day to 32 patients who had surgically removed stage I or II melanoma for three years. 49 patients were in the controlled group. Recombinant interferon alpha-2b was given throughout the trial to all patients. After five years, metastases had occurred in 26.5% of patients in the control group and in 3.1% of those receiving CoQ10 ($p = 0.006$).

- **Victor VM et.al.** [61] have made an attempt for a potential new therapeutic strategy for cardiovascular diseases by targeting antioxidants to Mitochondria. Mitochondria produce large amounts of free radicals and play an important role in the life and death of a cell. Thus, mitochondrial oxidative damage and dysfunction contribute to a number of cell pathologies that manifest themselves through a range of conditions including ischemia-reperfusion injury, sepsis, diabetes, atherosclerosis and consequently cardiovascular diseases. In fact, endothelial dysfunction, characterized by a loss of nitric oxide (NO) bioactivity, occurs early on in the development of atherosclerosis, and determines future vascular complications. This review considers the process of CVD from a mitochondrial perspective. In this review, they provide a summary of the cellular metabolism of reactive oxygen species (ROS) and its role in pathophysiological processes such as CVD, currently available antioxidants and possible reasons for their efficacy and inefficacy in ameliorating oxidative stress-mediated diseases; recent developments in mitochondrially-targeted antioxidants and their therapeutic potential for future treatment of CVDs.

- **David G. Warnock et.al.** [62] studied that 18,722 participants in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study, a population-based U.S. sample of individuals aged 45 years and older. In this sample, 4,764 individuals had CVD and 14,361 did not. CVD included previous myocardial infarction, stroke, or a history of cardiovascular procedures. Among subjects with CVD and CKD, an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 was associated with a 2.8 times increased risk of death from any cause compared with subjects without CKD or CVD. Anemia was associated with a 2.7 times increased risk. Microalbuminuria

was associated with a 2.6 times increased risk. Among subjects with CKD but not CVD, an eGFR below 60, anemia and microalbuminuria increased the risk of all-cause mortality by 46%, 70% and 80% respectively.

- **Armando Lindner, Bernard Charra et.al.** [63] have studied the survival experience of 39 patients receiving long-term regular hemodialysis with particular reference to mortality and morbidity from arteriosclerotic cardiovascular complications. Mean age (± 1 S.D.) was 37.0 ± 9.5 years for the group at the start of dialysis. Mean duration of treatment was 6.5 years. Overall mortality was 56.4% at the end of the 13-year follow-up period, and 14 of 23 deaths could be attributed to arteriosclerotic complications: MI was responsible for 8, strokes for 3, and refractory congestive heart failure for 3 deaths. The incidence of these complications was many times higher than for normal and hypertensive groups of comparable age, and similar to rates found in Type 2 hyperlipoproteinemia. These results indicate that accelerated atherosclerosis is a major risk to long-term survivors on maintenance hemodialysis.

- **Emma A. Meagher et.al.** [64] have conducted a Randomized, double-blind, placebo-controlled trial with 30 healthy men and women aged 18 to 60 years to assess the effects of supplemental vitamin E on lipid peroxidation in vivo in healthy adults. Participants were randomly assigned to receive placebo or a-tocopherol dosages of 200, 400, 800, 1200, or 2000 IU/d for 8 weeks (n=5 in each group), followed by an 8-week washout period. Three indices of lipid peroxidation, urinary 4-hydroxynonenal (4-HNE) and 2 isoprostanes, iPF2α-III and iPF2α –VI were and compared among the 6 groups at baseline, 2, 4, 6, and 8 weeks, and 1, 3, and 8 weeks after discontinuation. The results concludes the rationale for vitamin

E supplementation in healthy individuals. Specific quantitative indices of oxidative stress in vivo should be considered as entry criteria and for dose selection in clinical trials of antioxidant drugs and vitamins in human disease.

- **Herrera E et.al.** [65] have reviewed the action, metabolism and perspectives of Vitamin E. As vitamin E acts in cell membranes where it prevents the propagation of free radical reactions, it has been also shown to have pro-oxidant activity. Non-radical oxidation products are formed by the reaction between α-tocopheryl radical and other free radicals, which are conjugated to glucuronic acid and excreted through the bile or urine. In Liver, By the action of the "alpha-tocopherol transfer protein", a major proportion of alpha-tocopherol is incorporated into nascent very low density lipoproteins (VLDL), whereas the excess of alpha-tocopherol plus the other forms of vitamin E are excreted in bile. Once secreted into the circulation, VLDL are converted into IDL and LDL by the action of Lipoprotein Lipase (LPL), and the excess of surface components, including alpha-tocopherol, are transferred to HDL. Besides the LPL action, the delivery of alpha-tocopherol to tissues takes place by the uptake of lipoproteins by different tissues throughout their corresponding receptors.

- **Wang X et.al.** [66] reviewed the function of Vitamin E in membranes. Due to its lipophilic properties, it partitions into lipid storage organelles and cell membranes. It is, therefore, widely distributed in throughout the body. Vitamin E is believed to be involved in a variety of physiological and biochemical functions. The molecular mechanism of these functions is believed to be mediated by either the antioxidant action of the vitamin or by its action as a membrane stabiliser. α -Tocopherol is an efficient scavenger of lipid peroxyl radicals and, hence, it is

able to break peroxyl chain propagation reactions. The regeneration of α -tocopherol from its tocopheroxyloxyl radical greatly enhances the turnover efficiency of α-tocopherol in its role as a lipid antioxidant. The molecule is able to rotate about its long axis and diffuse laterally within fluid lipid bilayers. The vitamin does not distribute randomly throughout phospholipid bilayers but forms complexes of defined stoichiometry which coexist with bilayers of pure phospholipid. This fact would be expected to reduce the efficiency of the vitamin in its action as a lipid antioxidant and to destabilise rather than stabilise membranes.

- **Mustacich DJ et.al.** [67] reviewed that the most well-known function of vitamin E is that of a chain-breaking antioxidant that prevents the cyclic propagation of lipid peroxidation. Despite its antioxidant function, dietary vitamin E requirements in humans are limited only to alpha-tocopherol because the other forms of vitamin E are poorly recognized by the hepatic alpha-tocopherol transfer protein (TTP), and they are not converted to alpha-tocopherol by humans. In attempts to gain a better understanding of vitamin E's health benefits, the molecular regulatory mechanisms of vitamin E have received increased attention.

AIM OF THE STUDY

The aim of this study is

1. To find whether Vitamin E and Coenzyme Q 10 has lipid lowering effect in dyslipidaemic patients who receives Atorvastatin therapy.
2. To compare the level of changes in the serum lipid levels between a group treated with Atorvastatin (Group 1), a group treated with Vitamin E + Atorvastatin (Group 2) and a group treated with Coenzyme Q 10 + Atorvastatin (Group 3).
3. To compare the levels of changes in Random blood glucose and Blood Pressure between the groups treated with Atorvastatin (Group 1), a group treated with Vitamin E + Atorvastatin (Group 2) and a group treated with Coenzyme Q 10 + Atorvastatin (Group 3).

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METHODOLOGY

This study was performed in the cardiology department of Meenakshi Mission Hospital and Research Centre (MMHRC), Madurai, under the co-guidance of Dr. S. Selvamani, M.D., DNB (internal medicine)., DNB(cardiology) [interventional cardiologist].

Design of Study : Randomized Controlled Study

Sample Size : 60 patients

Study Duration : June 2013 – February 2014

No. of Groups : 3

Drugs Used

Group 1: Atorvastatin 40 mg/day (Storvas 40 mg tablets)

Group 2: Vitamin E 400 mg/day (Evion 400 soft gelatin capsules) + Atorvastatin 40 mg/day

Group 3: Coenzyme Q 10 30 mg/day (CoQ 30 soft gelatin capsules) + Atorvastatin 40 mg/day

Parameter Measured: Serum Lipid Profile

Inclusion Criteria

1. Patients who had serum lipid levels

   Total Cholesterol > 200 mg/dL

   LDL > 130 mg/dL

   HDL < 35 mg/dL

   Triglycerides > 170 mg/dL

   VLDL > 36 mg/dL

2. The patients who take Atorvastatin 40 mg/day

3. Patients whose age was in the range 30 to 70 years
4. Both Diabetic and Hypertensive patients were also included

Exclusion Criteria

1. Patients with hypersensitivity to Atorvastatin, Vitamin E and Coenzyme Q 10
2. Smokers
3. Pregnant and lactating women
4. Patients with Arrhythmias and Congestive Heart Failure
5. Patients taking any antioxidant other than Vitamin E and Coenzyme Q 10

Method of work

All the 60 patients enrolled for the study were divided in to three groups randomly. Group 1, Group 2 and Group 3. Their case history were collected and documented.

Then the baseline lipid profile was taken for all the 60 patients and documented. Then Group 1 patients treated with Atorvastatin 40 mg/ day / oral. Group 2 patients was taken Vitamin E 400 mg / day + Atorvastatin 40 mg / day orally. Group 3 patients received Coenzyme Q 10 30 mg/day + Atorvastatin 40 mg / day orally.

All the three groups of patients were monitored for compliance, and for ADRs. At the end of 4 months the lipid profile of the patients were taken again as the end point. Then the lipid profiles of Group 1, Group 2 and Group 3 were compared.

Statistical Tool

All the data were recorded in the Master Chart. The Data Analysis was done using GraphPad InStat DTCG (GPI v 3.0). Mean, Standard Deviation, Student unpaired t-test and 'p' values were calculated for quantitative variables. The 'p' values were two-tailed and obtained by using the student's unpaired t-test, with the standard deviations of each value to be different. 'p' value less than 0.05 was considered to imply a significant relationship.

The comparative charts were drawn using the mean of the values of different parameters.

OBSERVATION

Clinical Features

In the study, all three groups had various ranges of difference in age, sex, status of disorders, family history of dyslipidaemia, and smoking. So there was a requirement of distributions to ensure whether there is any significant influence from any of the foresaid factors.

All the patients of three groups had a wide range of serum lipid levels. So mean and standard deviation was calculated for all the values. The 'p' value of all the parameters were measured by considering the standard deviation of all the values to be different.

In Group 1 there were 6 diabetic patients, in Group 2 there were 10 diabetic patients and in Group 3 there were also 10 diabetic patients. They were already under anti-diabetic therapy. The reduction in random blood glucose was monitored for these patients only.

In addition, in the Group 1 there were 7 hypertensive patients, in Group 2 there were 6 hypertensive patients and in Group 3 there were 7 hypertensive patients. These patients were also under anti-hypertensive therapy. The reduction in blood pressure was monitored for these patients only. The reduction in systolic and diastolic pressure were monitored and tabulated separately.

The percentage change in lipid profile, random blood glucose, and blood pressure were also calculated. Charts were also drawn to easily assess the results. Mean value of the parameters were used to draw the charts.

Age Distribution

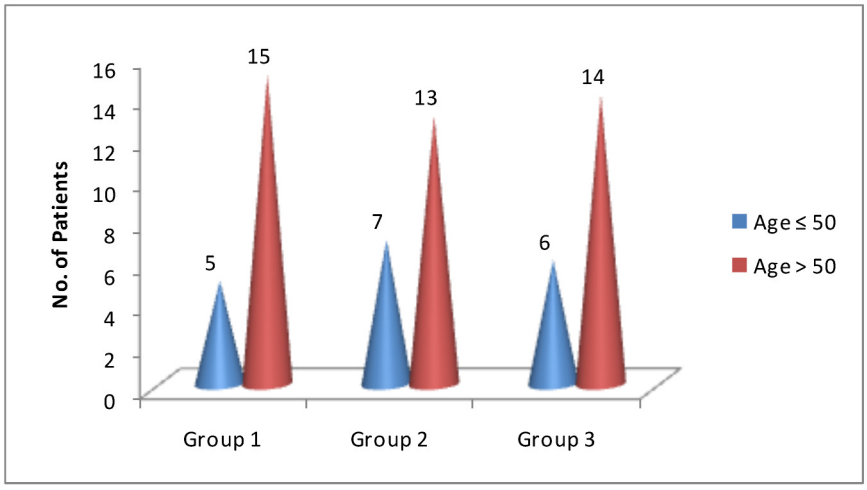
In this study, patients from the age limits of 30 and 70 years were enrolled. So there may be chances for the age to influence the results. So a distribution of age between the three groups were established. Table 7 and Fig. 2 represent the distribution.

Table 7. Age Distribution

Study Groups		Age (in years)		Total	'p' value
		≤ 50	> 50		
Group 2: Vitamin E 400 mg/day + Atorvastatin 40 mg/dayNo. of Patients Group 1: Atorvastatin 40 mg/ day	No. of Patients	7	13	20	
Group 3: Coenzyme Q 10 30 mg/day + Atorvastatin 40 mg/day	No. of Patients	6	14	20	

The 'p' value was greater than 0.05. It implies an insignificant relationship.

Fig. 2



Gender Distribution

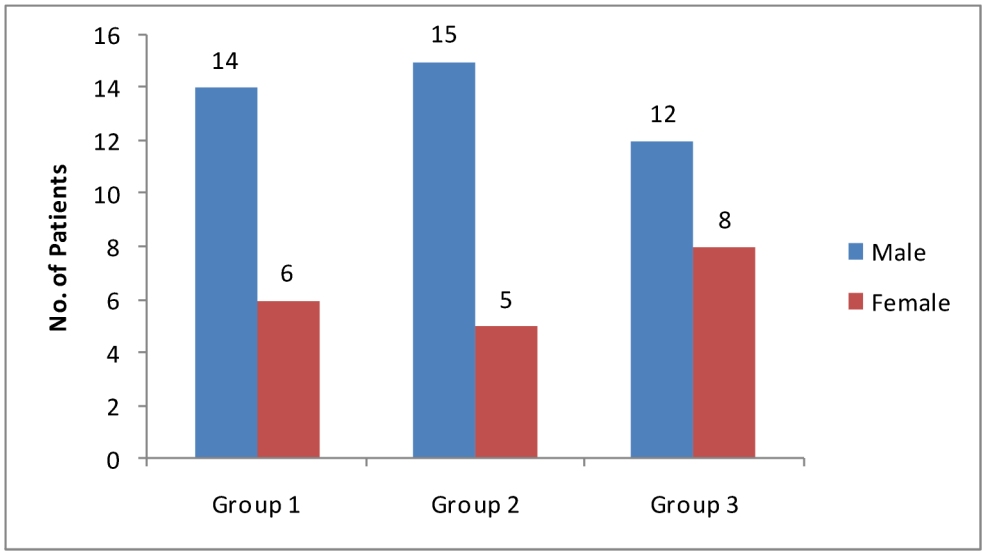
Group 1 had 14 male and 6 female patients, Group 2 had 15 male and 5 female patients. In Group 3 there are 12 male and 8 female patients.

Table 8. Gender Distribution

Study Groups		Gender		Total	'p' value
		Male	Female		
Group 1	No. of Patients	14	6	20	0.9631
Group 2	No. of Patients	15	5	20	
Group 3	No. of Patients	12	8	20	

The 'p' value was greater than 0.05. It implies an insignificant relationship.

Fig.3



Distribution for Diabetes mellitus

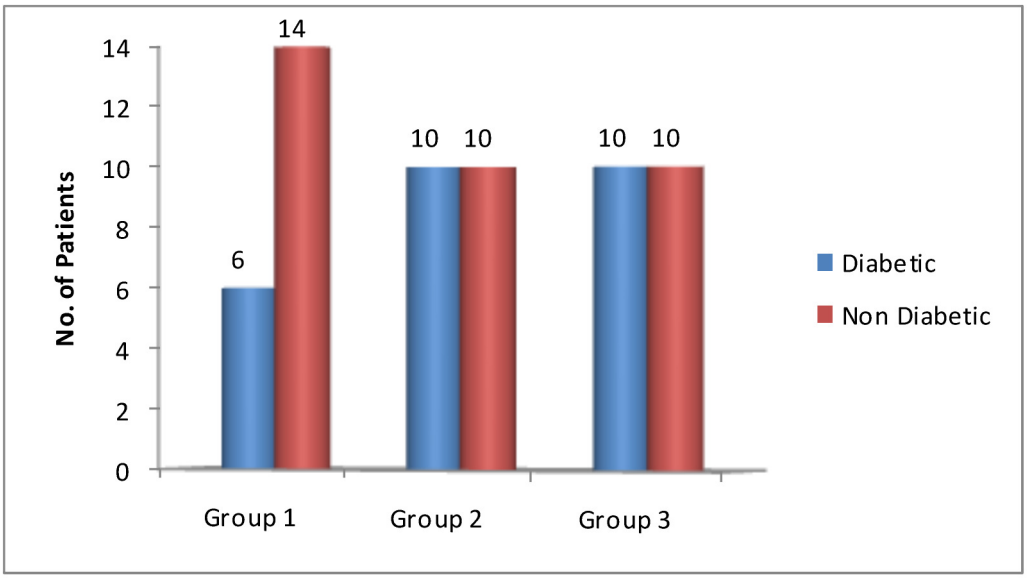
Group 1 had 6 diabetic patients, Group 2 had 10 diabetic patients and Group 3 also had 10 diabetic patients. A distribution was established to see whether the blood glucose level influence the results.

Table 9. Distribution for Diabetes mellitus

Study Groups		Diabetes Mellitus		Total	'p' value
		Diabetic	Non Diabetic		
Group 1	No. of Patients	6	14	20	0.5661
Group 2	No. of Patients	10	10	20	
Group 3	No. of Patients	10	10	20	

The 'p' value was greater than 0.05. It implies an insignificant relationship.

Fig. 4



Distribution for Hypertension

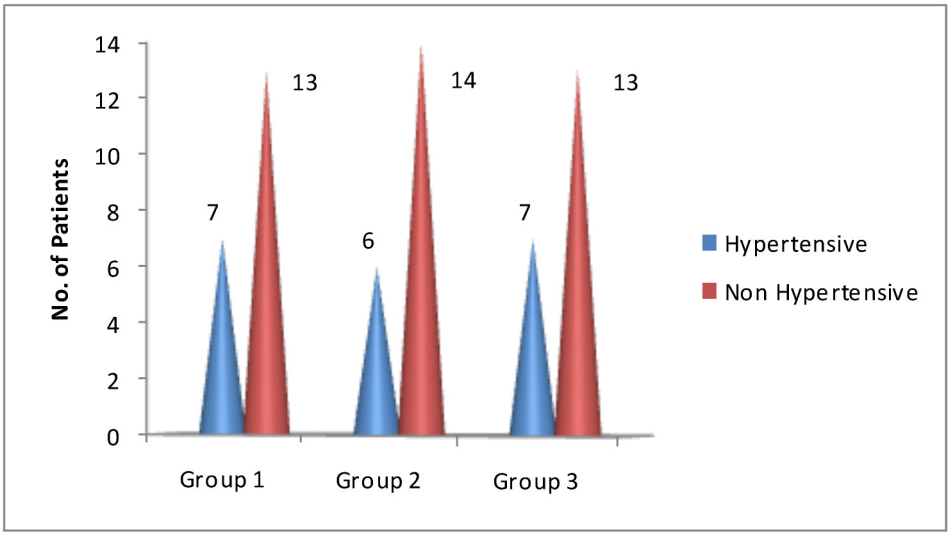
In this study Group 1, Group 2 and Group 3 had 7, 6 and 7 hypertensive patients respectively.

Table 10. Distribution for Hypertension

Study Groups		Hypertension		Total	'p' value
		Hypertensive	Non Hypertensive		
Group 1	No. of Patients	7	13	20	0.5732
Group 2	No. of Patients	6	14	20	
Group 3	No. of Patients	7	13	20	

The 'p' value was greater than 0.05. It implies an insignificant relationship.

Fig. 5



Distribution for Family History

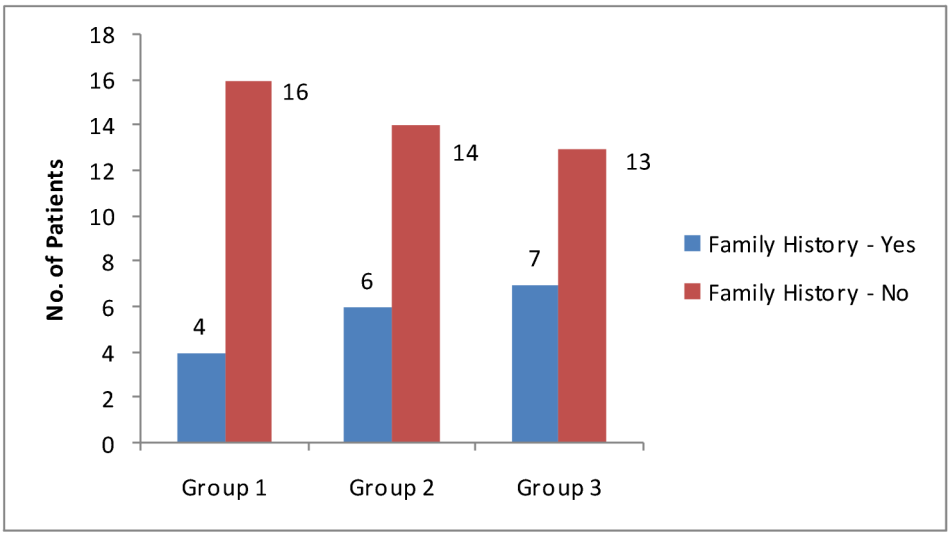
In Group 1, Group 2 and Group 3, 4, 7 and 6 patients had a family history of dyslipidaemia respectively.

Table 11. Distribution for Family History

Study Groups		Family History of Dyslipidaemia		Total	'p' value
		Yes	No		
Group 1	No. of Patients	4	16	20	0.7326
Group 2	No. of Patients	6	14	20	
Group 3	No. of Patients	7	13	20	

The 'p' value was greater than 0.05. It implies an insignificant relationship.

Fig. 6



Distribution for Smoking

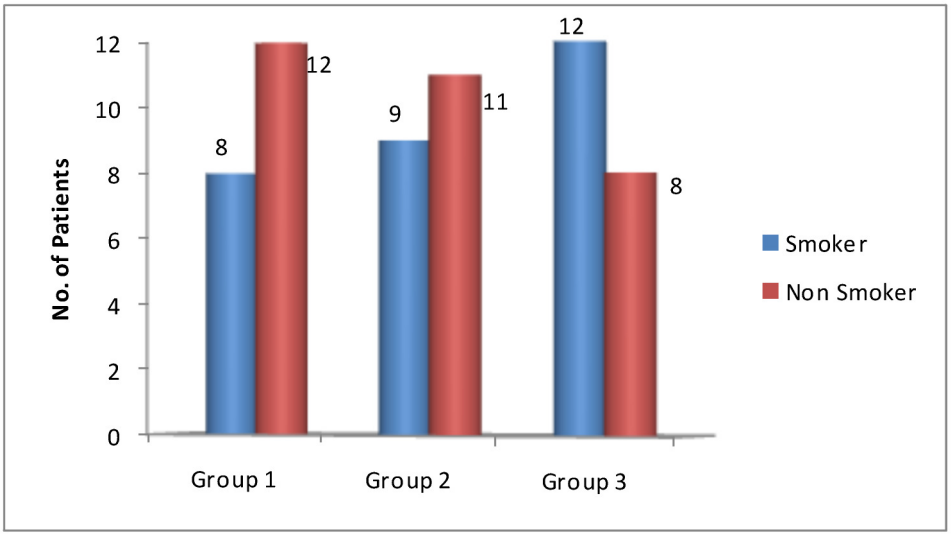
In Group 1, eight patients, in Group 2, nine Patients and in Group 3, twelve patients were smokers before starting this therapy.

Table 12. Distribution for Smoking

Study Groups		Smoker		Total	'p' value
		Yes	No		
Group 1	No. of Patients	8	12	20	0.8474
Group 2	No. of Patients	9	11	20	
Group 3	No. of Patients	12	8	20	

The 'p' value was greater than 0.05. It implies an insignificant relationship.

Fig. 7



Changes in Lipid Profile

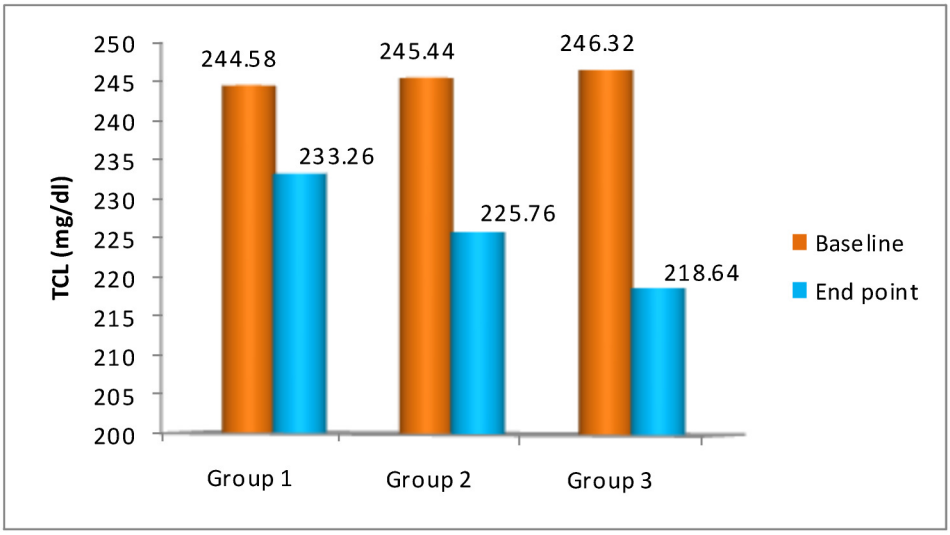
Changes in Serum Total Cholesterol Level

Fig.8 and Table 13 imply that the Mean change in serum total cholesterol level in all three Groups were significant.

Table 13. Changes in Serum Total Cholesterol Level

Study Groups	Serum Total Cholesterol (mg/dL) [mean]				'p' value
	Baseline	Endpoint	Difference	%	
Group 1	244.58 ± 18.57	233.26 ± 16.63	11.32	4.63	0.2427
Group 2	245.44 ± 19.14	225.76 ± 17.87	19.68	8.02	0.1456
Group 3	246.32 ± 22.82	218.64 ± 14.37	27.68	11.24	0.1040

Fig. 8



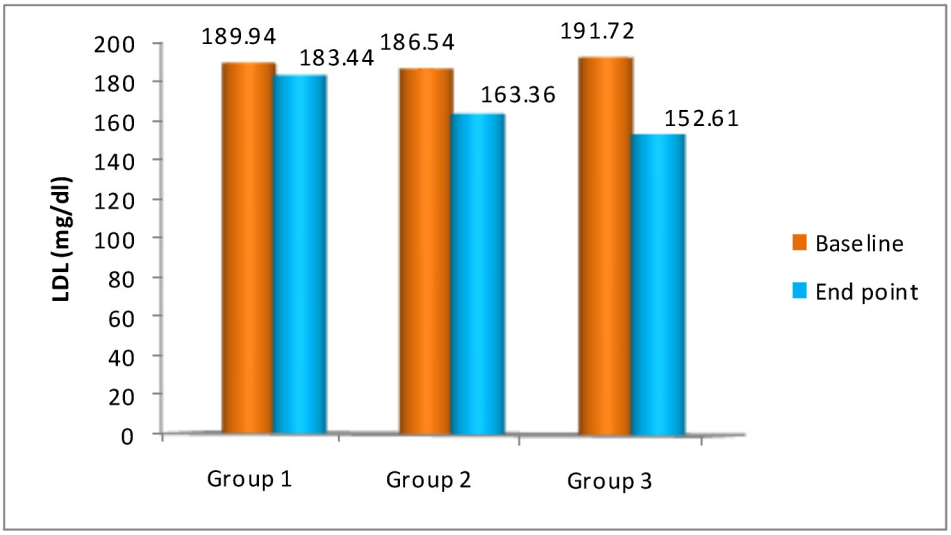
Changes in Serum LDL Level

Fig.9 and Table 14 imply that the Mean change in serum Low Density Lipid level in all three Groups were significant.

Table 14. Changes in Serum LDL Level

Study Groups	Serum LDL (mg/dL) [mean]				'p' value
	Baseline	Endpoint	Difference	%	
Group 1	189.94 ± 19.93	183.44 ± 20.19	6.50	3.42	0.3670
Group 2	186.54 ± 17.28	163.36 ± 14.57	23.18	12.43	0.0910
Group 3	191.72 ± 20.36	152.61 ± 18.65	39.11	20.40	0.0520

Fig.9



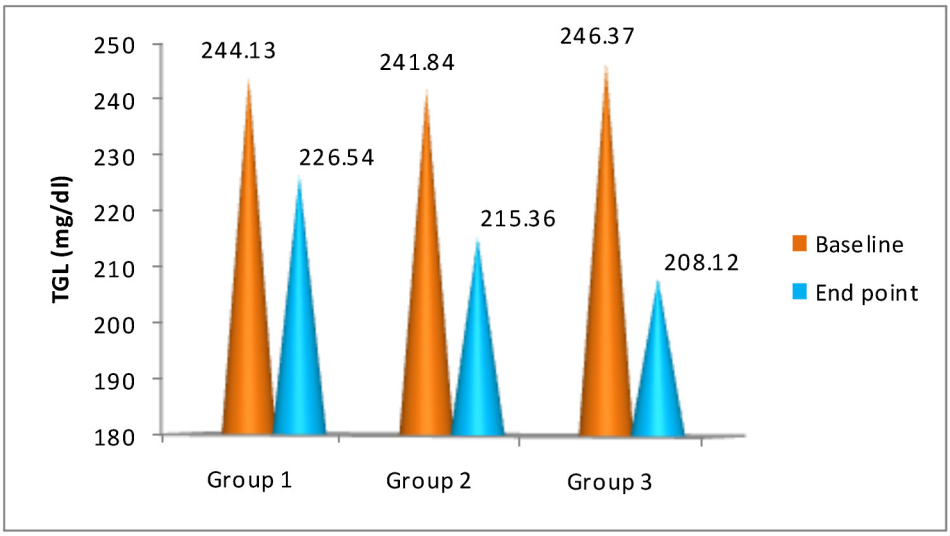
Changes in Serum Triglyceride Level

Fig.10 and Table 15 imply that the Mean change in serum Triglyceride level in all three Groups were significant.

Table 15. Changes In Serum Triglyceride Level

Study Groups	Serum Triglycerides (mg/dL) [mean]				'p' value
	Baseline	Endpoint	Difference	%	
Group 1	244.13 ± 43.36	226.54 ± 31.60	17.59	7.21	0.1821
Group 2	241.84 ± 38.69	215.36 ± 28.12	26.48	10.95	0.1214
Group 3	246.37 ± 42.62	208.12 ± 33.17	38.25	15.53	0.0775

Fig.10



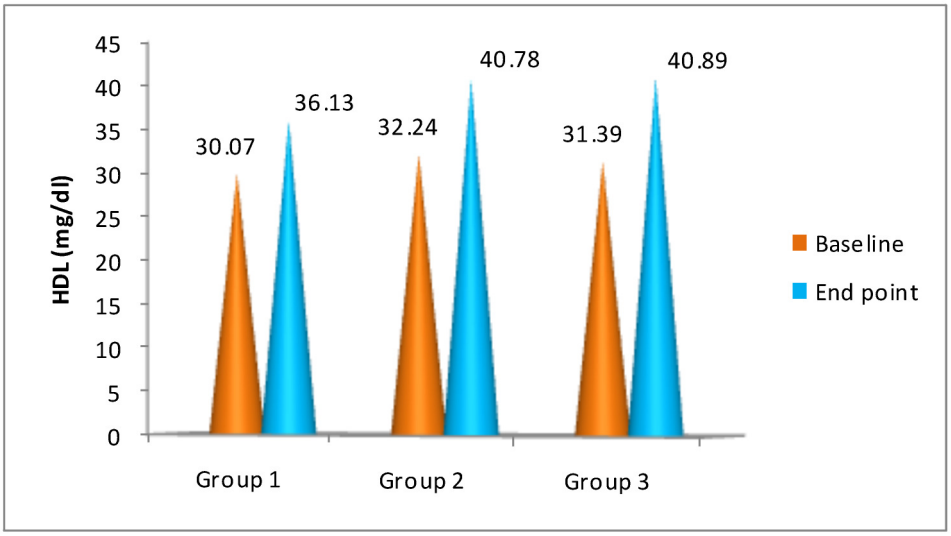
Changes in Serum HDL Level

Fig.11 and Table 16 imply that the Mean change in serum HDL level in Group 1, Group 2 and Group 3 were significant.

Table 16. Changes in Serum HDL Level

Study Groups	Serum HDL (mg/dL) [mean]				'p' value
	Baseline	Endpoint	Difference	%	
Group 1	30.07 ± 7.01	36.13 ± 6.13	6.06	20.15	0.0004
Group 2	32.24 ± 6.36	40.78 ± 4.88	8.54	26.49	0.0002
Group 3	31.39 ± 5.84	40.89 ± 5.22	9.50	30.26	0.0001

Fig. 11



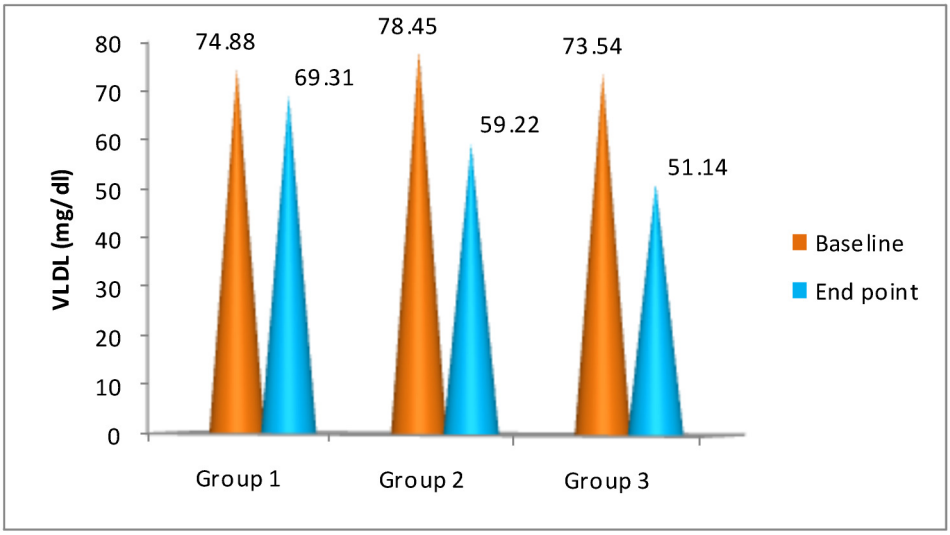
Changes in Serum VLDL Level

VLDL levels decreased in all the groups. Fig.12 and Table 17 imply that the Mean change in serum VLDL levels in Group 1 was insignificant. Whereas Group 2 and Group 3 were significant.

Table 17. Changes in Serum VLDL Level

Study Groups	Serum VLDL (mg/dL) [mean]				'p' value
	Baseline	Endpoint	Difference	%	
Group 1	74.88 ± 34.08	69.31 ± 32.28	5.57	7.44	0.6391
Group 2	78.45 ± 31.62	59.22 ± 30.18	19.23	24.51	0.1826
Group 3	73.54 ± 35.41	51.14 ± 28.80	22.40	30.46	0.1522

Fig.12



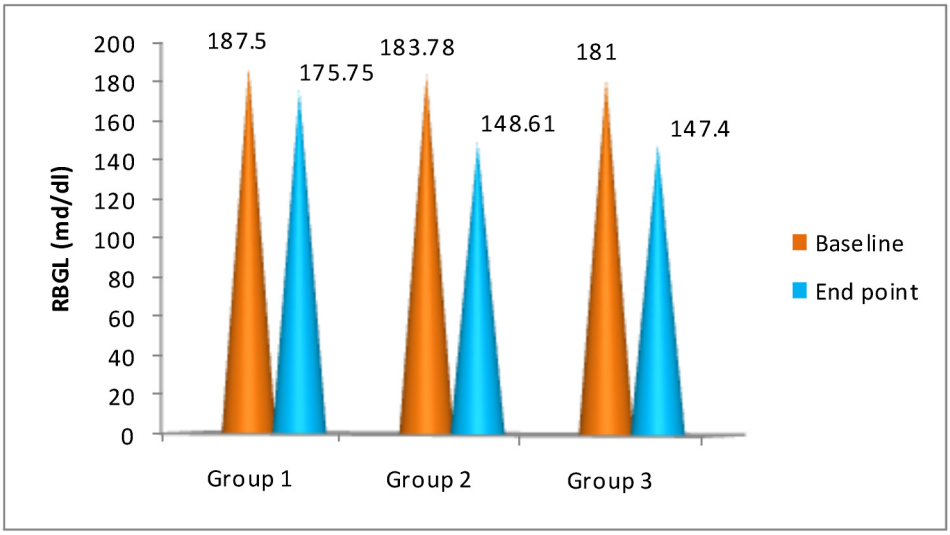
Changes in Random Blood Glucose Level

Fig.13 and Table 18 imply that the Mean change in random blood glucose level in Group 1 was insignificant and that of Group 2 was significant.

Table 18. Changes in Random Blood Glucose Level

Study Groups	Random Blood Glucose (mg/dL) [mean]				'p' value
	Baseline	Endpoint	Difference	%	
Group 1	187.5 ± 33.24	175.75 ± 33.32	11.75	6.27	0.4926
Group 2	183.78 ± 30.14	148.61 ± 32.20	35.17	19.14	0.0378
Group 3	181.0 ± 35.74	147.40 ± 34.18	33.60	18.56	0.0464

Fig. 13



Changes in Blood Pressure Readings

Fig.14 and Table 19 show that the Mean change in Systolic Blood Pressure Reading in Group 1, Group 2 and Group 3 were significant.

Table 19. Changes in Blood Pressure Readings (Systolic)

Study Groups	Blood Pressure (mm Hg) [mean]				'p' value
	Baseline	Endpoint	Difference	%	
	Systolic	Systolic			
Group 1	152.14 ± 8.59	147.6 ± 8.33	4.54	2.98	0.3792
Group 2	156.64 ± 8.61	133.3 ± 7.89	23.34	14.90	0.0485
Group 3	154.38 ± 6.78	140.5 ± 6.74	13.88	8.99	0.1425

Fig. 14

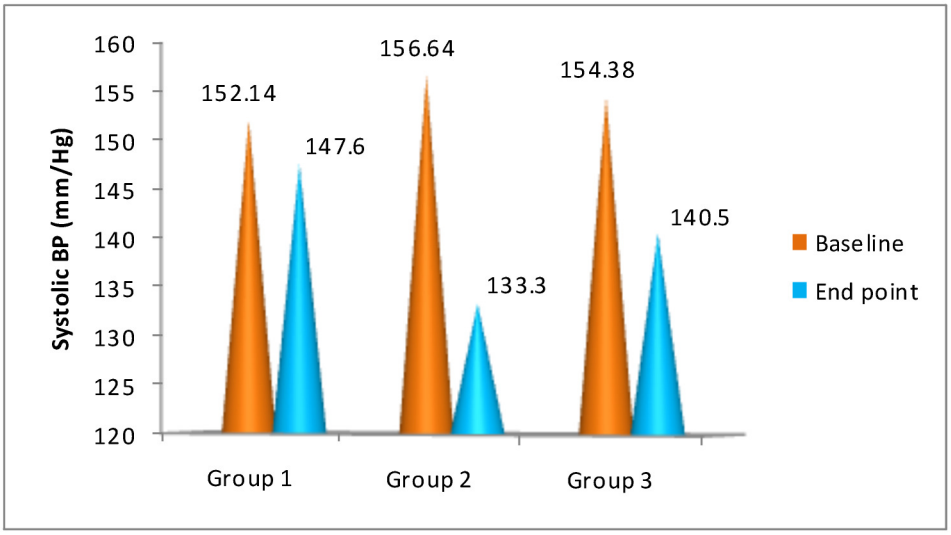
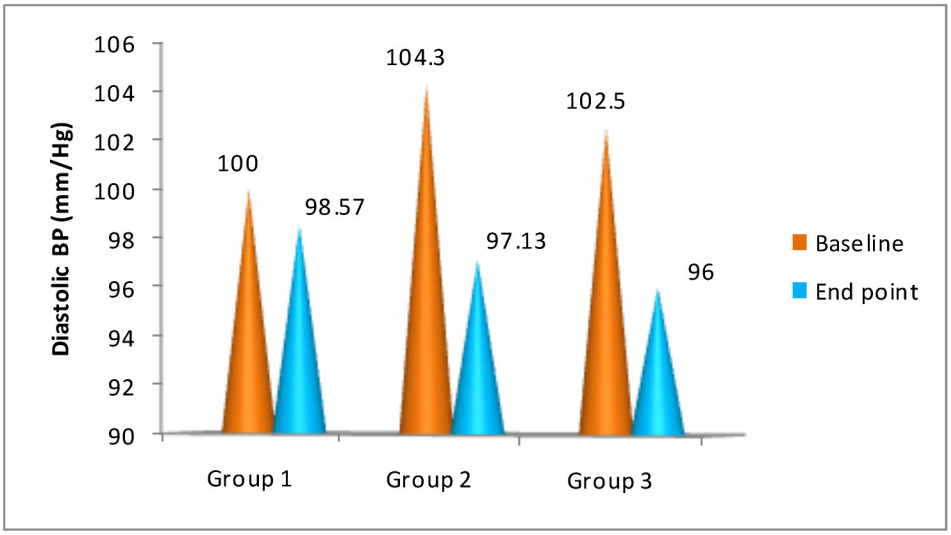


Fig.15 and Table 20 show that the Mean change in Diastolic Blood Pressure Reading in Group 1was insignificant and that of Group 2 was not quite significant.

Table 20. Changes in Blood Pressure Readings (Diastolic)

Study Groups	Blood Pressure (mm Hg) [mean]				'p' value
	Baseline Diastolic	Endpoint Diastolic	Difference	%	
Group 1	100 ± 8.16	98.57 ± 7.46	1.43	1.43	0.739
Group 2	104.3 ± 6.18	97.13 ± 6.92	7.17	6.87	0.062
Group 3	102.5 ± 7.07	96 ± 6.07	6.50	6.34	0.073

Fig. 15



RESULTS AND DISCUSSION

In this study Group 3 shows excellent reduction in serum Total Cholesterol than Group 2 and Group 1. Group 2 shows better reduction in serum Total Cholesterol than Group 1 (Table 13).

The reduction in serum LDL level in Group 3 was higher than that of Group 2 and Group 2 was higher than that of Group 1 the reduction was found to be statistically significant (Table 14).

The reduction in serum triglyceride level in Group 3 was higher than that of Group 2 and Group 2 was higher than that of Group 1 the reduction was found to be statistically significant (Table 15).

The increase in serum HDL level in Group 3 was higher than that of Group 2 and Group 2 was higher than that of Group 1 the reduction was found to be statistically significant (Table 16).

The reduction in serum VLDL level in Group 3 was higher than that of Group 2 and Group 2 was higher than that of Group 1 the reduction was found to be statistically significant (Table17).

The reduction in random blood glucose level in Group 3 was higher than that of Group 2 and Group 2 was higher than that of Group 1 the reduction was found to be statistically significant (Table18).

7. a. The reduction in systolic blood pressure in Group 3 was higher than that of Group 2 and Group 2 was higher than that of Group 1 the reduction was found to be statistically significant (Table 19).

b. The reduction in diastolic blood pressure in Group 3 was higher than that of Group 2 and Group 2 was higher than that of Group 1 the reduction was found to be statistically significant (Table 20).

In this study 30 mg/day of Coenzyme Q 10 was given to the patients of Group 3. The observation shows that the baseline lipid profiles have improved at the end of the study.

Group 1 showed 4.63 % reduction in serum total cholesterol (Table 13). This reduction may be due to the Atorvastatin 40 mg taken by the patients. In Group 2, there was an 8.02 % reduction of the same. This additional reduction may be due to the adjuvant therapy with Vitamin E. But In Group 3, there was an 11.24 % reduction of TCL. This is due to the adjuvant therapy with Coenzyme Q 10. Statistically the difference showed significance (Table 13). By this it can be said that reduction in serum total cholesterol is more significant only when Atorvastatin is given in combination with Coenzyme Q 10.

The reduction of serum LDL level (Table 14) in Group 3 was again much higher than that in Group 2 and Group 1. In Group 1 the reduction was only 3.42 %, in Group 2 the reduction was 12.43 % and in Group 3, the reduction 20.40 %. Statistically the reduction in serum LDL in Group 3 is significant (Table 14) when compared with that of Group 2 and Group 1.This implies that LDL reduction is powerful when Atorvastatin and Coenzyme Q 10 combination is given.

In Group 1 the reduction in the serum triglyceride level (Table 15) was 7.21 %, in Group 2 it was 10.95 %. But in Group 3 reduction was 15.53 %. The difference in reduction was statistically significant (Table 15). This again states that Atorvastatin and Coenzyme Q 10 combination is preferable.

The increase in the serum HDL level (Table 16) in Group 1 was 20.15 %. In group 2 26.49 % but in Group 3 serum HDL was 30.26 %, and it was statistically significant (Table 16). This implies that Coenzyme Q 10 can have a significant effect in increasing serum HDL levels when it is given with a HMG CoA reductase inhibitor. This

shows that there is a special mechanism by which Coenzyme Q 10 increases serum HDL level.

The reduction of serum VLDL level (Table 17) in Group 3 was higher than that of other two Groups. In Group 1 the reduction was 7.44 %, in Group 2 the reduction was 24.51 %. But in group 3 reduction was 30.46 %. This reduction was found to be statistically significant (Table 17). This again proves a combination of Statin and Coenzyme Q 10 highly effective in lipid lowering effect.

Apart from lipid lowering the hypoglycaemic effect of Coenzyme Q 10 was also monitored. It revealed that Coenzyme Q 10 has considerable anti-diabetic effect, and the 'p' value expressed significance (Table 18). Group 3 also showed a considerable reduction in systolic B.P. and it was statistically significant (Table 19). But the diastolic blood pressure in Group 2 shows very significant reduction (Table 20).

On the whole the comparison of reduction in lipid parameters shows that Atorvastatin + Coenzyme Q 10 combination has a powerful lipid lowering effect, when compared to Atorvastatin + Vitamin E combination and Atorvastatin alone.

CONCLUSION

As per the observations and results we can conclude that Coenzyme Q 10 possess lipid lowering effect in dyslipidaemic patients.

Coenzyme Q 10 reduces serum total cholesterol and serum LDL, and increases serum HDL when given in combination with Atorvastatin. It also shows marked influence in reducing the random blood glucose and blood pressure.

Currently Coenzyme Q 10 is not prescribed by physicians for lowering serum lipid levels, because of inadequate studies on the lipid lowering effect of Coenzyme Q 10, and the cost of the medication. Each 30 mg capsule of Coenzyme Q 10 is Rs.19.

But, considering its therapeutic efficacy, safety, and other beneficial effects, Coenzyme Q 10 can be recommended for prescription to dyslipidaemic patients.

Appendix

Patient Profile Format

Name: **Sex:** **D.O.B. & Age:**

Weight: **Height:** **Nationality:**

Residential Address:

Contact No.:

Hospital No.:

Medical History:

Medication History:

Sensitivity to Drugs:

Lipid profile:

Serum Lipid Level (mg/dL)	Total Cholesterol	LDL	Triglycerides	HDL	VLDL
Base-line					
End-point					

Random Blood Glucose:

Base-line:

End-point:

Blood Pressure:

Blood Pressure	Systolic	Diastolic
Base-line		
End-point		

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